NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sBLA
Application Number(s)	BLA 761180, Efficacy Supplement-S001
Priority or Standard	Standard
Submit Date(s)	January 14, 2022
Received Date(s)	January 14, 2022
PDUFA Goal Date	February 14, 2023
Division/Office	Division of Dermatology and Dentistry, Office of Immunology and Inflammation
Review Completion Date	
Established/Proper Name	Tralokinumab
(Proposed) Trade Name	ADBRY
Pharmacologic Class	IgG4 monoclonal antibody that neutralizes IL-13 cytokine by inhibiting interactions with IL-13 receptors α1 and α2
Code name	CAT-354
Applicant	LEO Pharma A/S
Doseage form	Solution for Injection
Applicant 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. 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 (as per current PI)
Applicant Proposed Indication(s)/Population(s)	For the treatment of moderate-to-severe atopic dermatitis in patients ≥ 12 years of age whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. ADBRY can be used with or without topical corticosteroids.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	24079001 |Atopic dermatitis (disorder)
Recommendation on Regulatory Action	Complete Response (CR)
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of moderate-to-severe atopic dermatitis in patients ≥ 12 years of age whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. ADBRY can be used with or without topical corticosteroids
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	24079001 |Atopic dermatitis (disorder)

Recommended Dosing Regimen	Adults (≥ 18 years of age): initial dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) administered every other week. A dosage of 300 mg every 4 weeks may be considered for patients below 100 kg who achieve clear or almost clear skin after 16 weeks of treatment. Adolescents (12 to <18 years of age): initial dose of 300 mg (two 150 mg injections), followed by 150 mg administered every other week. In children 12 years of age and older, it is recommended that ADBRY be given by or under supervision of an adult.

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Strother D. Dixon
Nonclinical Reviewer	NA
Nonclinical Team Leader	NA
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Clinical Reviewer	Hamid Tabatabai, MD
Clinical Team Leader/ Cross-Disciplinary Team Leader	David Kettl, MD
Statistical Reviewer	Marilena Flouri, PhD
Statistical Team Leader	Mohamed Alosh, PhD
Deputy Director for Safety	Tatiana Oussova, MD, MPH

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DMEPA=Division of Medication Error Prevention and Analysis
DMPP= Division of Medical Policy Programs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology and Pharmacometrics Reviewer	Da Zhang, PhD	Division of Inflammation and Immune Pharmacology (DIIP)	Sections 6 and 19.5	Select one: __x_ Authored ___ Approved
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Pharmacometrics Team Leader	Youwei Bi, PhD	DIIP	Sections 6 and 19.5	Select one: ___ Authored _X__ Approved
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Clinical Reviewer	Hamid Tabatabai, MD	Office of Immunology and Inflammation (OII)/Division of Dermatology and Dentistry (DDD)	Sections: 1, 2, 3, 4.1, 7, 8.2, 8.3.2, 8.4, 9, 10, 11, 12, 13, 19.2	Select one: _X_ Authored ___ Approved
	Signature: See DARRTS for signatrure			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	David Kettl, MD	OII/DDD	Sections: 1, 2, 3, 4.1, 7, 8.2, 8.3.2, 8.4, 9, 10, 11, 12, 13, 19.2	Select one: ___ Authored _X__ Approved
	Signature: See DARRTS for signature			
Statistical Reviewer	Marilena Flouri, Ph.D.	Division of Biometrics III (DB III)	Sections: 8.1, 8.3.1, 19.3	Select one: _X__ Authored ___ Approved
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Statistical Team Leader	Mohamed Alosh, Ph.D.	DB III	Sections: 8.1, 8.3.1, 19.3	Select one: ___ Authored _X__ Approved
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Deputy Director for Safety	Tatiana Oussova, MD, MPH .	OII/DDD	Sections: All	Select one: ___ Authored _X__ Approved
	Signature: See DARRTS for signature			

Glossary

AC	advisory committee
AD	atopic dermatitis
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ANCOVA	analysis of covariance
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDLQI	Children's Dermatology Life Quality Index
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
LOCF	observation carried forward
MAR	missing at random

MAS	maintenance analysis set
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MTP	multiplicity testing procedure
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NRI	non-responder imputation
NRS	numeric rating scale
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert (also known as Patient Information)
PPS	per-protocol set
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PYE	Patient-years of Exposure
Q2W	every 2 weeks
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SCORAD	Scoring Atopic Dermatitis
SGE	special government employee
SOC	standard of care
TCI	topical calcineurin inhibitor
TCS	Topical Corticosteroids
TEAE	treatment emergent adverse event
WOCF	worst observation carried forward

1 Executive Summary

1.1. Product Introduction

ADBRY (tralokinumab) is an IgG4 Anti-IL-13-Rα1/α2 monoclonal antibody licensed by the FDA on 12/27/2021 for the indication of treatment (with or without topical corticosteroids) 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.

The Applicant (LEO Pharma A/S) submitted a Prior Approval Efficacy Supplement (S-001) under The regulatory pathway 351(a) of the Public Health Service Act to broaden the patient population from "adult patients" to "patients aged 12 years and older" (with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable) in labeling upon approval of this supplement. ADBRY can be used with or without topical corticosteroids.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Trial LP0162-1334 (ECZTRA 6) , supporting efficacy supplement S-001, was conducted in adolescent (12 years ≤ age ≤17 years) subjects with moderate to severe atopic dermatitis (defined as baseline affected BSA≥ 10%, EASI score ≥16, IGA = 3 (moderate) or 4 (severe), WI-NRS (weekly average)≥ 4, and Body weight ≥ 30 kg) with history of topical corticosteroid (TCS) or topical calcineurin inhibitor (TCI) treatment failure or subjects for whom these topical AD treatments are medically inadvisable. This trial had a 16-week placebo-controlled period, a 36-week maintenance/open-label treatment period, and a 14-week safety follow-up period.

The primary efficacy endpoint for this trial was the proportion of subjects achieving IGA response (IGA score of 0 (clear) or 1 (almost clear) [which included a ≥2-grade reduction from Baseline]). A key secondary efficacy endpoint was EASI75 at Week 16, and a secondary efficacy endpoint (pre-specified and controlled for multiplicity, for which the Applicant seeks labeling claims) was the proportion of subjects worst pruritus NRS response (weekly average) of ≥4-point improvement from baseline at Week 16.

Substantial evidence of efficacy was demonstrated based on the analysis of the results from the primary efficacy endpoints. Analysis of the results from the secondary efficacy endpoint was supportive of efficacy.

As noted below, however, due to the dosing administration recommendations for the adolescent population, additional information was requested from the Applicant. The requested Human Factor study results were submitted January 5, 2023, and will need to be reviewed in a second cycle. These data will provide supporting information regarding the user

interface and human factors information for the 150 mg Q2W dose, showing that 150 mg Q2W dosing can be used safely in the adolescent population. Due to the timing of this submission so close to the goal date, a Complete Response will be recommended for this supplement and the submitted Human Factors information will need to be considered in a subsequent cycle to allow approval of tralokinumab in the adolescent population.

The determination that 150 mg Q2W dosing can be used safely in the adolescent population cannot be made prior to the goal date and a Complete Response is recommended.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit-risk profile of tralokinumab for the treatment of moderate to severe atopic dermatitis (AD) in adolescent subjects (12 years to 17 years of age, inclusive) is favorable, based on data from one adequate and well-controlled clinical trial (ECZTRA 6). This trial enrolled 289 adolescent subjects with moderate to severe AD.

- Efficacy: tralokinumab (300 mg followed by 150 mg every 2 weeks dose group) was statistically superior to the placebo for the following primary and secondary efficacy endpoints (prespecified in the protocol and controlled for multiplicity), for the Full Analysis Set (FAS) [includes all subjects randomized and dosed, excluding trial sites 340 and 341] at Week 16:

  i. For the primary efficacy endpoint of IGA response (IGA score = 0 or 1 [which includes a ≥ 2-grade reduction from baseline]), the tralokinumab group achieved a response of 21.4%, compared to 4.3% for the placebo group (95% CI: 8.4%-26.6%), a treatment effect of 17.5% (P-value < 0.001).
  ii. For the key secondary efficacy endpoint of EASI-75, the tralokinumab group achieved a response of 28.6%, compared to 6.4% for the placebo group (95% CI: 12.4%-32.6%), a treatment effect of 22.5% (P-value < 0.001).
  iii. For the secondary efficacy endpoint of worst daily pruritus NRS (≥ 4-points improvement from baseline), the tralokinumab group achieved a response of 23.2%, compared to 3.3% for the placebo group (95% CI: 10.6%-29.9%), a treatment effect of 19.9% (P-value < 0.001).

- Efficacy results for tralokinumab (600 mg followed by 300 mg every 2 weeks dose group) was statistically superior to the placebo for the following primary and secondary efficacy endpoints for the FAS at Week 16:

  i. For the primary efficacy endpoint of IGA response, the tralokinumab group achieved a response of 17.5%, compared to 4.3% for the placebo group (95% CI: 5.3%-22.3%), a treatment effect of 13.8% (P-value = 0.002).
  ii. For the key secondary efficacy endpoint of EASI-75, the tralokinumab group achieved a response of 27.8%, compared to 6.4% for the placebo group (95% CI: 12.0%-32.0%), a treatment effect of approximately 22.0% (P-value < 0.001).

iii. For the secondary efficacy endpoint of worst daily pruritus NRS (≥ 4-points improvement from baseline), the tralokinumab group achieved a response of 25.0%, compared to 3.3% for the placebo group (95% CI: 12.3%-31.1%), a treatment effect of approximately 21.7% (P-value < 0.001).

• Safety: Analysis of the primary safety database for trial ECZTRA 6 did not identify any new safety signals, was qualitatively similar to the analysis of safety data from clinical trials for tralokinumab conducted for adult subjects, and was adequate to characterize the safety profile of tralokinumab for the treatment of moderate to severe AD in adolescent subjects. Adverse Reactions reported through Week 16 in ≥ 1% of subjects treated with tralokinumab at 300 mg followed by 150 mg every 2 weeks (and ≥1% more frequently than subjects receiving placebo) compared to subjects treated with placebo included Conjunctivitis cluster [Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial] (4.1% vs. 2.1%), Injection sites reaction cluster [Injection site edema, Injection site pain, Injection site reaction, Injection site swelling, Injection site urticaria] (9.2% vs. 1.1%), Upper respiratory tract infection cluster [Nasopharyngitis, Pharyngitis, Upper respiratory tract infection, Viral upper respiratory tract infection] (27.6% vs. 18.1%), headache (5.1% vs. 3.2%), insomnia (3.1% vs. 1.1%), nausea (3.1% vs. 0), cystitis (2.0% vs. 0), and skin infection (2.0% vs. 0).

The available results support extension of the age group for the indication of "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" to include patients aged 12 years and older in the "Indications and Usage Section" of the label, inclusion of the efficacy data from trial ECZTRA 6 in sections 14 of the label, and inclusion of safety conclusions for trial ECZTRA 6 summarized in the following statement in Sec. 6 of the ADBRY label: "The safety of tralokinumab was assessed in a trial of 289 subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (ECZTRA 6). The safety profile of ADBRY in these subjects, assessed through the initial treatment period of 16 weeks and the long-term period of 52 weeks, was similar to the safety profile from trials in adults with atopic dermatitis".

Tralokinumab offers an alternative treatment option for adolescent patients with moderate to severe atopic dermatitis whose disease are not adequately manageable by topical therapies, and for whom treatment options are limited. Because treatment of this patient population who are candidates for treatment with a systemic product may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options for this subgroup of patients with atopic dermatitis.

The review team identified no safety or efficacy issues that would preclude approval of supplement S-001, and recommended an initial dose of tralokinumab 300 mg followed by 150 mg every 2 weeks in adolescent subjects. An IR was conveyed to the Applicant on 12/19/2022 to provide information on their plan to revise the user interface (e.g., IFU and labeling) to address the two different dosing regimens for the adult and

adolescent patient populations and submit additional human factors (HF) information. On 1/5/2023 (SDN 257), the Applicant provided supporting information regarding the user interface and human factors information for the 150 mg Q2W dose (to demonstrate that 150 mg Q2W dosing can be used safely in the adolescent population), was submitted shortly before the goal date and DMEPA will review this Human Factors information in a subsequent cycle. Therefore, DDD recommends a Complete Response (CR) for this efficacy supplement (S-001) for this review Cycle.

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). • 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 7.3% (Chiesa Fuxench et al. 2019).	• 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
	• Comorbidities may include asthma, allergic rhino-conjunctivitis, and food allergies.	
Current Treatment Options	• For the Applicant's target population of moderate-to-severe AD, available FDA-approved systemic treatments included dupilumab and corticosteroids at the time of the initial BLA licensure for tralokinumab (ADBRY) on 12/27/2021. Several Janus Kinase (JAK) Inhibitor oral drug products have since been Approved by the FDA for the treatment of refractory, moderate-to-severe AD in this population. • 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 (non-melanoma and melanoma), and cataracts. • Dupilumab is recommended for patients unresponsive to topical therapy for whom phototherapy is not feasible, with concomitant topical corticosteroids as needed. • The American Academy of Dermatology recommends that systemic corticosteroids generally be avoided because of the potential for short- and long-term adverse reactions. • 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. • 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 of the S-001 Efficacy Supplement for tralokinumab (ADBRY) would represent an important addition to the treatment options for adolescent patients (12 to < 18 years of age) with moderate-to-severe AD that is not manageable by topical therapies; a population for whom approved treatment options are limited. • Tralokinumab would be another systemic product approved for the treatment of moderate-to-severe AD in adolescent patients, following the approval of dupilumab, abrocitinib and upadacitinib, (other than corticosteroids). Tralokinumab would represent an alternative to dupilumab and upadacitinib for systemic treatment of moderate-to-severe AD. Corticosteroids, although approved, are not generally recommended for this indication. Upadacitinib use in adolescent patients with moderate-to-severe AD will be reserved for refractory patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Upadacitinib (Rinvoq) [for patients ≥ 12 years of age], and Abrocitinib (Cibinqo) [for adult patients] were Approved by the FDA on 1/14/2022 for the treatment of patients with refractory, moderate-to-severe AD whose disease are not adequately controlled with other systemic drugs, including Biologics, or when use of those therapies are inadvisable. •	
Benefit	• The efficacy of tralokinumab was demonstrated in trial ECZTRA-6. Tralokinumab was statistically superior to placebo for the two primary endpoints of IGA success (defined as scoring 0 or 1) and EASI-75 at Week 16, as well as for the secondary endpoint of improvement in the Worst Daily Pruritus NRS score (weekly average) of ≥ 4-point reduction from baseline at Week 16.	• Tralokinumab clearly demonstrated activity in patients with AD in adequate and well-controlled trials. • The clinical trial design and endpoints were appropriate for the AD population, for which there are limited treatment options.
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 adolescent (12 ≤ age < 18 years) subjects with AD is primarily based on the results from the Phase 3 trial, ECZTRA 6. • No deaths were reported during trial ECZTRA 6. • The safety database was adequate to assess risks and outcomes. In trial ECZTRA 6, 195 subjects were treated with subcutaneous injections of tralokinumab in the initial period; and a total of 264 subjects received tralokinumab (at different doses and dosing frequency) during the maintenance or open-label treatment periods for a total duration of up to 52 weeks (247 subjects completed Week 52 visit). • The most common adverse reactions (reported in (≥3% of subjects in	• Based on the available data, tralokinumab has a favorable safety profile and would be acceptable for approval for licensure of this supplement for the adolescent patients. • The safety database was adequate for comprehensive safety assessment of tralokinumab for the proposed indication, patient population, dosage regimen, and duration of treatment. • Safety risks have not been identified that require risk management beyond standard pharmacovigilance. A REMS is not recommended for this supplement. • Clinical trial report LP0162-1334 (ECZTRA 6) submitted under the Prior Approval Supplement (S-001) is also intended to

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the combined dose groups during the initial period) were upper respiratory infections, atopic dermatitis, injection site reaction/injection site pain, headache, and conjunctivitis; and was consistent with the AE profile previously reported in the AD pool for adult subjects. • In trial ECZTRA 6, the incidence of Anti-drug antibodies (ADA)/ Neutralizing antibodies (nAb) during the initial 16-week treatment period was similarly low in the adolescent and adult trial populations . • In trial ECZTRA 6, 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).	fulfil the requirements of the PREA PMR 4015-1 issued by the FDA at the time of initial licensure for this BLA on 12/27/2021. No additional PREA PMRs will be required for this supplement. Due to the dosing administration recommendations for the adolescent population, additional information was requested from the applicant. The requested Human Factor study results were submitted January 5, 2023 and will need to be reviewed in a second cycle. These data will provide supporting information regarding the user interface and human factors information for the 150 mg Q2W dose, showing that 150 mg Q2W dosing can be used safely in the adolescent population. Due to the timing of this submission so close to the goal date, a Complete Response will be recommended for this supplement and the submitted Human Factors information will need to be considered in a subsequent cycle to allow approval of tralokinumab in the adolescent population. The determination that 150 mg Q2W dosing can be used safely in the adolescent population cannot be made prior to the goal

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		date and a Complete Response is recommended.

1.4. Patient Experience Data

Secondary endpoints in ECZTRA-6 trial included the following patient-reported outcome assessments during the initial treatment period from baseline to Week 16:

1. Reduction of Worst Daily Pruritus numeric rating scale (NRS) score (weekly average) ≥4 points.
2. Change in Scoring Atopic Dermatitis (SCORAD) score- includes both patient-reported and Investigator-reported assessments).
3. Change in Children's Dermatology Life Quality Index (CDLQI) score.
4. Change in Patient-Oriented Eczema Measure (POEM)
5. Change in Eczema-related Sleep NRS
6. Change in Hospital Anxiety and Depression Scale (HADS) total score.

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	sBLA submission (SDN 64), M 2.7.3, Panels 8 and 9.
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			

	□	Input informed from participation in meetings with patient stakeholders	
	X	Patient-focused drug development or other stakeholder meeting summary reports	Externally Led PFDD Meeting on Atopic Dermatitis held at College Park Marriott, Hyattsville, Maryland on 9/23/2019
	□	Observational survey studies designed to capture patient experience data	
	□	Other: (Please specify):	
□	Patient experience data was not submitted as part of this application.		

Abbreviations: sBLA, supplemental biologics license application; PFDD, patient-focused drug development.

2 Therapeutic Context

2.1. Analysis of Condition

Atopic dermatitis 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. Although it may affect all age groups, AD is most common in children. In 60% of patients, the onset of disease is in the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals[1].[1] Shaw et al. reported the prevalence of AD in the United States in individuals 4-8 years of age to be 10.63% and in those 9-12 years of age to be 9.96%[2]. For 10-30% of individuals, AD persists into the adult years[3].

AD 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). In patients older than 2 years of age, the presentation is similar to that in adults. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, wrists, and volar aspects of the Wrists[1]. AD may be generalized.

The pathogenesis involves a complex interplay of genetic, immunological, and environmental factors that result in abnormal skin barrier function and immune system dysfunction[3]. Irregularities in the terminal differentiation of the epidermal epithelium lead to a faulty stratum corneum which permits the penetration of environmental allergens[4]. The exposure to allergens may ultimately result in systemic sensitization and may predispose AD patients to other conditions, such as asthma and food allergies.[4]

Acute AD is associated with cytokines produced by T helper type 2 (Th2) cells (as well as other

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[1] Weston WL and Howe W. Atopic dermatitis (eczema): Pathogenesis, clinical manifestations, and diagnosis of atopic dermatitis. Dellavalle RP, Levy ML, Fowler J, eds. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on April 15, 2020).

[2] Shaw TE et al. Eczema prevalence in the United States: Data from the 2003 National Survey of Children's Health. J Invest Dermatol. (2011) 131, 67–73.

[3] Eichenfield LF et al. Guidelines of care for the management of atopic dermatitis Section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014;70:338-51.

[4] Leung DYM, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: Shifting paradigms in treatment approaches. J Allergy Clin Immunol 2014;134:769-79.

T-cell subsets and immune elements)[4]. These cytokines are thought to play an important role in the inflammatory response of the skin, and IL-4 and IL-13 may have distinct functional roles in Th2 inflammation[5]. IL-4 has been shown to stimulate immunoglobulin E (IgE) production from B cells[6]. IL-13 expression correlates with disease severity and flares[4]. IL-4 mediates its biological activity via binding to IL-4Rα. IL-13 receptor alpha 1 (IL-13Rα1) may then be recruited to form a signaling complex. IL-13 mediates its biological activity via binding to IL-13Rα1 and subsequent recruitment of IL-4Rα, forming a signaling complex[6]. IL-4 and IL-13 reside on chromosome 5q23-31, among a grouping of genes related to development of allergic diseases[6]. Dupilumab inhibits IL-4 and IL-13 by blocking the shared IL-4Rα subunit[7]. Tralokinumab binds to human IL-13 and inhibits its interaction with the IL-13Rα1, IL-13Rα2, and IL-13Rα1/IL-4Rα receptor complex[8].

Common comorbidities include asthma, allergic rhinitis/rhino-conjunctivitis, and food Allergies[1,3]. Comorbidities involving the eyes include atopic keratoconjunctivitis[1], a chronic, intensely pruritic, allergic disease that is most often seen in adults with AD[9]. Patients with AD often experience sleep disturbance, largely attributable to the associated extreme pruritus. The disruption in sleep could have carryover effects to impact behavior and neurocognitive functioning[10]. Sleep disturbance in the affected individual may also disrupt the sleep of family members, impacting the quality of life for all[10]. Affected children may experience depression and anxiety[11], social isolation[12], and impaired psychosocial functioning[1,12].

Patients with AD are predisposed to colonization or infection by microbes, particularly *Staphylococcus aureus* and herpes simplex virus. The susceptibility to *S. aureus* is related to multiple factors, including the abnormal skin barrier function and the production of serine proteases that degrade the skin barrier[4].

The most common laboratory finding is an elevated IgE[2]. Up to 80% of the AD population has elevated IgE, often with accompanying eosinophilia[1]. IgE levels may fluctuate with disease severity; however, some patients with severe AD present with normal IgE levels[1].

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[5] Bao K and Reinhardt RL. The differential expression of IL-4 and IL-13 and its impact on type-2 Immunity. Cytokine 75 (2015) 25-37.

[6] May RD, Fung M. Strategies targeting the IL-4/IL-13 axes in disease. Cytokine 2015;75:89-116.

[7] DUPIXENT package insert.

[8] ADBRY package insert.

[9] Hamrah P and Dana R. Atopic keratoconjunctivitis. Trobe J, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on April 16, 2020).

[10] Camfferman D et al. Eczema and sleep and its relationship to daytime functioning in children. Sleep Medicine Reviews 14 (2010) 359–369.

[11] Yaghmaie P et al. Mental health comorbidity in patients with atopic dermatitis. J Allergy Clin Immunol 2013;131:428-33.

[12] Drucker AM et al. The burden of atopic dermatitis: summary of a report for the National Eczema Association. J Invest Dermatol (2017) 137, 26-30.

2.2. Analysis of Current Treatment Options

The Food and Drug Administration (FDA)-approved or FDA-licensed treatments for AD fall in the categories of corticosteroids (topical and systemic), calcineurin inhibitors (topical), phosphodiesterase-4 (PDE-4) inhibitors (topical), IL-4 receptor antagonist (dupilumab), IL-13 antagonist (tralokinumab), and Janus Kinase Inhibitors (JAKi) (topical and oral).

Prior to the licensure of dupilumab and tralokinumab and approval of oral Janus Kinase Inhibitors (JAKi) [upadacitinib and abrocitinib for treatment of patients with refractory AD], corticosteroids were the only systemically-administered products that were FDA-approved for treatment of an AD indication in any age group.

Corticosteroids are available for treatment of AD by various routes of administration, including topical, oral, and parenteral. Although their use may result in rapid improvement, the AD commonly recurs with worse severity on discontinuation of the systemic corticosteroids (rebound). For this reason and because of the potential for adverse effects, the American Academy of Dermatology recommends that systemic steroids generally be avoided in the treatment of AD because potential risks generally outweigh the benefits[13]. Potential adverse effects include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia and other endocrine effects. A particular concern in children and adolescents is the risk of decreased linear growth during treatment[13]. Labels for systemic corticosteroids do not specify any limitations on the age of indication.

Topical corticosteroids (TCS) represent the cornerstone of anti-inflammatory treatment of AD in all age groups[14]. Numerous TCS, in various dosage forms and potencies, are available for treatment of AD, and some are specifically indicated for pediatric use. For example, fluticasone propionate lotion, 0.05%, a medium potency TCS, is indicated for relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 3 months of age and older. According to product labels, TCS may be sufficiently absorbed to lead to systemic adverse effects. Additionally, pediatric patients may be more susceptible to systemic toxicity doses due to their larger skin surface to body mass ratios. Labeled potential local adverse effects include skin atrophy, striae, telangiectasias, and hypopigmentation.

The topical calcineurin inhibitors (TCI), tacrolimus ointment and pimecrolimus cream, are also

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[13] Sidbury et al. Guidelines of care for the management of atopic dermatitis. Section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol 2014;71:327-49.
[14] Eichenfeld et al. Guidelines of care for the management of atopic dermatitis. Section 1. Management and treatment with topical therapies. J Am Acad Dermatol 2014;71:116-32.

indicated for treatment of AD in pediatric patients (2 years and older): tacrolimus for moderate to severe AD, and pimecrolimus for mild to moderate AD. However, both are labeled for second-line, short-term use when other topical prescription treatments have failed or are inadvisable. The calcineurin inhibitors carry boxed warnings advising that the safety of their long-term use has not been established. More specifically, the boxed warnings describe that rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors; a causal relationship has not been established.

Crisaborole ointment, 2%, a PDE-4 inhibitor, is approved for treatment of AD in pediatric patients (3 months of age and older). However, the product is indicated for a somewhat different AD population (mild to moderate AD) than the target population for Tralokinumab (moderate to severe AD). Nonpharmacologic care is critical to AD management and includes attention to bathing practices and the regular use of moisturizers, which are available in several delivery systems, such as creams, ointments, oils, lotions[14]. Moisturizers are directed at the xerosis and transepidermal water loss that are central elements of the disease[14]. They may also relieve pruritus, lessen erythema and fissuring, and improve lichenification[14]. Moisturizers themselves may be the principal treatment for mild disease. Although there are no standardized or universal recommendations regarding the use of moisturizers, repeated application of generous amounts is thought to be important and required, irrespective of the severity of disease[14]. The use of moisturizers during maintenance may stave off flares and may lessen the amounts of pharmacologic agents needed to control the disease[14].

Tralokinumab is currently indicated for use in patients ≥ 18 years of age with moderate to severe AD. The Applicant proposes broadening the use of tralokinumab to allow for the treatment of patients ≥ 12 years of age who have failed topical therapies or when those therapies are inadvisable. Specifically, the Applicant proposes tralokinumab for "patients 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable." FDA-approved systemic treatment options are limited for this patient population, consisting only of corticosteroids and dupilumab; their limitations have been discussed above.

Phototherapy (UVA and UVB) is considered safe and effective treatment for AD patients who are candidates for systemic therapy, including children[13]. However, phototherapy may require frequent in-office visits (e.g., several times a week) and time missed from school (and also, possibly from work for caregivers). Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn-like reactions (erythema, tenderness, pruritus), skin cancer (nonmelanoma and melanoma), and cataracts[13]. However, long-term risks from phototherapy treatment of AD in children have not been evaluated[13]. Narrowband UVB therapy may be considered first-line because of the safety profile relative to psoralen + UVA (PUVA)[13].

Systemic immunomodulating agents are used off-label to treat AD, including in pediatric patients, include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil[13]. The reported effectiveness for the products varies from "efficacious" (cyclosporine) to

"inconsistent" (mycophenolate mofetil)[13]. Similarly, the safety profiles vary, although each product carries the potential for significant adverse effects, and all of these product labels include boxed warnings. A small sampling of labeled risks includes nephrotoxicity (cyclosporine), cytopenias (azathioprine), hepatotoxicity (methotrexate), and embryofetal toxicity (mycophenolate mofetil)[15].

[15] Sections 2.1/2.2 of this review were adapted from review of sNDA 761055/S-020 (Dupilumab) on 5/22/2020 by Brenda Carr, MD; updates, including references to tralokinumab and JAK Inhibitors were added by this reviewer.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

ADBRY (tralokinumab) was developed under IND 123797 submitted on 11/5/2014 for the proposed indication of treatment of AD and was licensed by the FDA on 12/27/2021 under the regulatory pathway 351(a) of the Public Health Service Act.

At the time of submission for this supplement, the limited postmarketing data for adult patients (available from Germany from ADBRY' s date of approval in July 2021 to the data cut-off date of 9/30/2021) and from an early access program in France did not indicate new safety concerns.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed ADBRY for the treatment of moderate to severe AD under the 351(a) regulatory pathway. To fulfill a Pediatric Research Equity Act Postmarketing Requirement (PREA PMR 4015-1) associated with the original BLA approval on 27 December 2021, the Applicant conducted a Clinical Trial in subjects between 12 to 17 years of age (LP0162-1334, ECZTRA 6) entitled: "Tralokinumab monotherapy for adolescent subjects with moderate-to-severe atopic dermatitis".

Milestone interactions with the Applicant (related to supplement S-001: Study LP0162-1334, ECZTRA 6) included the following:

- Advice letters related to the Statistical Analysis Plan (SAP) on 9/21/2018, 10/24/2018, 3/29/2019, and 10/8/2021.
- Advice letters related to the pruritus WI-NRS on 12/20/2017, and adolescent PROs on 10/16/2018.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate. The Applicant excluded clinical trial sites 340 (n=2) and 341 (n=7) for GCP noncompliance, and subjects from these sites were excluded from the primary analysis population in the modified statistical analysis plan (SAP). The analyses of the safety and efficacy data were not affected in a meaningful way by exclusion of these two sites and support the conclusion that trial ECZTRA 6 was conducted adequately. The data generated support the proposed indication in the target population.

The OSI inspected the following two clinical trial sites in support of this supplement:

1. Tracy Bridges, M.D., Site #312 (n=10), Albany, GA.
   Inspection of this site revealed one data discrepancy but concluded that the study overall appears to have been conducted adequately, and the data generated by this site appear to be acceptable in support of the respective indication.

2. Brock Andersen, M.D., Site #340 (n=2), Fruitland, ID.
   This site was selected based on the GCP noncompliance noted in the clinical study report by the Applicant. No data from this site was included in the analyses. An AE of herpes outbreak in Subject 1 at week 44 was not documented as an AE because the subject had had a past history of herpes. A Form FDA 483, Inspectional Observations, was issued to the clinical investigator (CI), and a response to the Form FDA 483 was received by the OSI. The CI provided a corrective action and/or a preventative action for future studies for each observation cited.

Refer to the OSI's Clinical Inspection Summary review by Elena Boley, MD, MBA (dated 16 September 2022) in DARRTS for additional details.

4.2. Product Quality

See Product Quality Review dated January 18, 2023.

4.3. Clinical Microbiology

NA

4.4. Devices and Companion Diagnostic Issues

NA

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This program used the currently licensed Adbry (tralokinumab) product and no new nonclinical information was submitted for this supplement.

6 Clinical Pharmacology

6.1. Executive Summary

Tralokinumab is a fully human recombinant monoclonal antibody of the immunoglobulin G4 (IgG4) subclass that specifically neutralizes the IL-13 cytokine by inhibiting interaction with the IL-13 receptors.

Tralokinumab (ADBRY™) was approved on December 27, 2021, 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 can be used with or without topical corticosteroids. The approved dosing regimen of tralokinumab (ADBRY™) is an initial dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) administered every other week. A dosage of 300 mg every 4 weeks may be considered for patients below 100 kg who achieve clear or almost clear skin after 16 weeks of treatment.

In this supplemental BLA (sBLA), the Applicant proposed to update the prescribing information and expand the use of tralokinumab to adolescent patients 12-17 years of age for the treatment of moderate-to-severe AD. This is based on the results of the completed trial of tralokinumab monotherapy in adolescent subjects with moderate-to-severe AD (ECZTRA 6, LP0162-1334). The clinical trial report for this Required Pediatric Assessment under Pediatric Research Equity Act (PREA) is also intended to fulfill the Post-marketing Requirement (PMR) 4015-1 associated with the BLA approval letter:

> 4015 –1 Study LP0162-1334 (ECZTRA 6): Efficacy and safety (phase 3, randomized, double blind, placebo controlled, parallel-group, monotherapy) study in adolescents 12 to <18 years of age with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic treatment.

The clinical pharmacology review focused on the appropriateness of the proposed dosing regimen for the treatment of AD in adolescent patients 12 to 17 years of age.

The key review issues with specific clinical pharmacology recommendations and comments are summarized in Table 1.

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Table 1. Summary of Clinical Pharmacology Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The effectiveness of tralokinumab, administered at 150 mg and 300 mg every other week, was established at Week 16 through a randomized, double blind, placebo controlled, parallel-group, monotherapy study (ECZTRA 6) in treating adolescent subjects with moderate-to-severe AD. There was no difference in the efficacy of the 150 mg dose versus the 300 mg dose. Hence the 150 mg dose is recommended for approval.
General dosing instructions	Tralokinumab is recommended to be administered to adolescents 12 to < 18 years of age by subcutaneous injection at an initial dose of 300 mg (two 150 mg injections) followed by 150 mg administered every other week.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dosage adjustment in any adolescent patient subgroups (e.g., age, sex or body weight) is needed.
Labeling	Refer to Section 6.2.2.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the pivotal clinical study.
Immunogenicity	Antibodies to tralokinumab were not associated with clinically relevant changes in serum tralokinumab concentrations and reduced efficacy.

6.1.1. Recommendation

The office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology has reviewed the relevant Clinical Pharmacology information provided by the Applicant in sBLA 761180 S001 for AD in adolescents 12 to <18 years of age and recommends approval of this sBLA from a clinical pharmacology perspective.

6.1.2. PMR Recommendation

No new PMR recommendations with this supplement. The PREA PMRs issued with the original BLA would apply.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics (PK)

The PK of tralokinumab in adolescent subjects with AD was evaluated in the 52-week phase 3 trial ECZTRA 6. The systemic exposure observed in this trial was higher than that observed in trials with adults with AD, which is likely related to the lower mean body weight in the adolescent subjects. In ECZTRA 6, the serum trough concentrations of tralokinumab observed for the 150 mg and 300 mg doses at both dosing regimens of Q2W and Q4W were consistent with the dose proportional PK behavior that was observed in adult patients with AD.

The tralokinumab population PK (popPK) model that was developed based on data from 10 clinical trials in adult subjects has been updated to include data from the adolescent subjects in ECZTRA 6 and CD-RI-CAT-354-1054 (a single dose phase 1 trial in adolescent subjects with asthma). The results of this analysis are generally consistent with those obtained for the adult population in the original model and no clinically relevant impact on the systemic exposure to tralokinumab was demonstrated for any of the covariates tested except for body weight. Based on the popPK analysis, body weight was identified as a statistically significant covariate, with steady state exposure to tralokinumab decreasing with increase body weight. When adjusted for body weight, the model accounted for most of the observed difference in exposure between adolescents and adults.

Pharmacodynamics (PD)

The biomarker results in adolescent subjects with AD are also consistent with those reported in adults. In ECZTRA 6, with both doses of tralokinumab (150 mg and 300 mg), reductions of both blood biomarkers (C-C motif chemokine ligand (CCL) CCL17, human interleukin (IL) IL-22 and immunoglobulin (Ig) IgE) and skin biomarkers (levels of short-chain lipids in lesional skin) were estimated. The clinical relevance of these biomarkers is not fully understood as it was not explored.

Immunogenicity

The immunogenicity results observed for the adolescent subjects in ECZTRA 6 are comparable with those reported for the adult population. The proportion of subjects with treatment-emergent ADA is marginally higher in ECZTRA 6, this trend was also observed in the placebo-treated subjects. Anti-drug antibody (ADA) titers and the rate of neutralizing antibody (nAb) were similarly low in the adolescent and adult trial populations and were deemed not to have an impact on the PK, efficacy, or safety of tralokinumab.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The sponsor proposed dosing regimen of tralokinumab in adolescents 12 to <18 years of age with moderate-to-severe AD [redacted] However, [redacted] clinical pharmacology has recommended the approval of an initial dose of 300 mg (two 150 mg injections) followed by 150 mg administered every other week. Therapeutic Individualization

No dose adjustment is necessary for any specific populations. Outstanding Issues

None

Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following recommendations on the labeling (Table 2):

Table 2 Tralokinumab Drug Labeling Recommendations

Applicant Proposed Update	Reviewer's Recommendations
HIGHLIGH OF PRESCRIBING INFORMATION **----------DOSAGE AND ADMINISTRATION----------** [redacted]	HIGHLIGH OF PRESCRIBING INFORMATION **----------DOSAGE AND ADMINISTRATION----------** The recommended dosage of ADBRY is: Adults: [redacted] Adolescents of 12 to <18 years of age: an initial dose of 300 mg (two 150 mg injections), followed by 150 mg administered every other week. (2.2)
2.2 Recommended Dosage [redacted]	2.2 Recommended Dosage The recommended dosage for adults and adolescents (12 Years and Older) is:

[redacted] (b) (4)	[redacted] (b) (4) The recommended dosage for adolescents (12 Years and older) is: • An initial dose of 300 mg (two 150 mg injections), followed by 150 mg administered every other week. • In children 12 years of age and older, it is recommended that ADBRY be given by or under supervision of an adult.
12.2 Pharmacodynamics ADBRY was associated with decreased concentrations of Th2 and Th22 immunity biomarkers in the blood, such as thymus and activation-regulated chemokine (TARC/CCL17), periostin, IL-22, lactate dehydrogenase (LDH) and serum IgE. ADBRY decreased expression of keratin 16 and Ki-67 in AD skin, and upregulated protein expression of loricrin. ADBRY suppressed expression of genes in the Th2 pathway, including CCL17, CCL18 and CCL26 as well as markers of Th17- and Th22-regulated genes in lesional skin. (b) (4) [redacted] The clinical relevance of these biomarkers is not fully understood.	12.2 Pharmacodynamics ADBRY was associated with decreased concentrations of Th2 and Th22 immunity biomarkers in the blood, such as thymus and activation-regulated chemokine (TARC/CCL17), periostin, IL-22, lactate dehydrogenase (LDH) and serum IgE. ADBRY decreased expression of keratin 16 and Ki-67 in AD skin, and upregulated protein expression of loricrin. ADBRY suppressed expression of genes in the Th2 pathway, including CCL17, CCL18 and CCL26 as well as markers of Th17- and Th22-regulated genes in lesional skin. (b) (4) [redacted] The clinical relevance of these biomarkers is not fully understood.
12.3 Pharmacokinetics … Pediatric Patients (b) (4) [redacted]	12.3 Pharmacokinetics … Pediatric Patients In adolescents 12 to 17 years of age with atopic dermatitis, the mean (SD) steady-state trough

[redacted]	concentration of tralokinumab-ldrm was [redacted] 59.6 mcg/mL (19.4) following administration of ADBRY at [redacted] 150 mg every other week.

6.3. Comprehensive Clinical Pharmacology Review

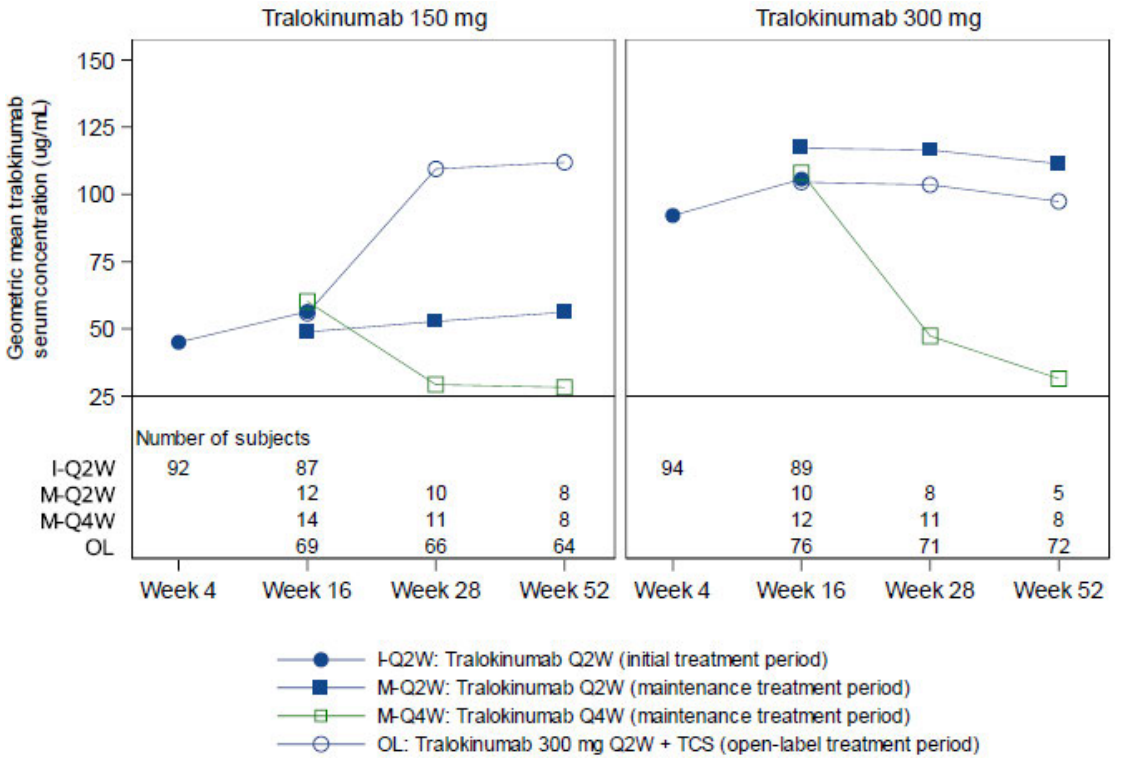
6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Phase 3 Trail (ECZTRA 6):

ECZTRA6 was a randomized, double-blind, placebo-controlled, parallel-group trial in adolescent subjects with moderate-to-severe AD. The primary objective was to evaluate the efficacy of tralokinumab in adolescents with moderate-to-severe AD during an initial 16-week treatment period. The trial also included a range of secondary, maintenance, and other objectives to further evaluate the efficacy of tralokinumab along with the safety, tolerability, immunogenicity, PK, and PD, including serum and skin biomarkers.

Figure 1 shows the geometric mean trough concentrations of tralokinumab over time for the different dosing regimens.

Figure 1 ECZTRA 6 – mean trough concentrations of tralokinumab after subcutaneous dosing every 2 or 4 weeks for up to 52 weeks, shown by initial treatment (150 mg or 300 mg)



Source: Panel 4. Module 2.7.2 Summary of clinical pharmacology addendum

For the subjects receiving tralokinumab 150 mg Q2W in the initial treatment period (left side of Figure 1), tralokinumab serum concentrations had reached steady state by Week 16. For the responders who were re-randomized at Week 16 to maintenance treatment with tralokinumab 150 mg Q2W, the trough concentration remained stable throughout the maintenance period (filled blue squares). For the responders who were re-randomized to Q4W, the trough concentration was approximately halved by the next sampling time point at Week 28 (open green squares), consistent with dose proportional PK. The benefit of Q4W dosing is inconclusive due to very low number of subjects.

For the subjects receiving tralokinumab 300 mg Q2W in the initial treatment period (right side of Figure 1), the pattern in the initial and maintenance treatment periods was similar to that described for 150 mg Q2W, with trough concentrations approximately the double of those in the corresponding tralokinumab 150 mg groups. (See more detailed PK results in the Appendix of Individual Study Review).

During the initial treatment period, 7 (7.1%) of the subjects treated with tralokinumab 150 mg, none of the subjects treated with tralokinumab 300 mg, and 2 (2.1%) of the subjects treated with placebo had treatment-emergent ADA. 2 (0.7%) tralokinumab-treated subjects tested

positive for nAb, which was deemed not to have an impact on the PK, efficacy, or safety of tralokinumab for these subjects. ADA titers were generally low, ranging from <10–320. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

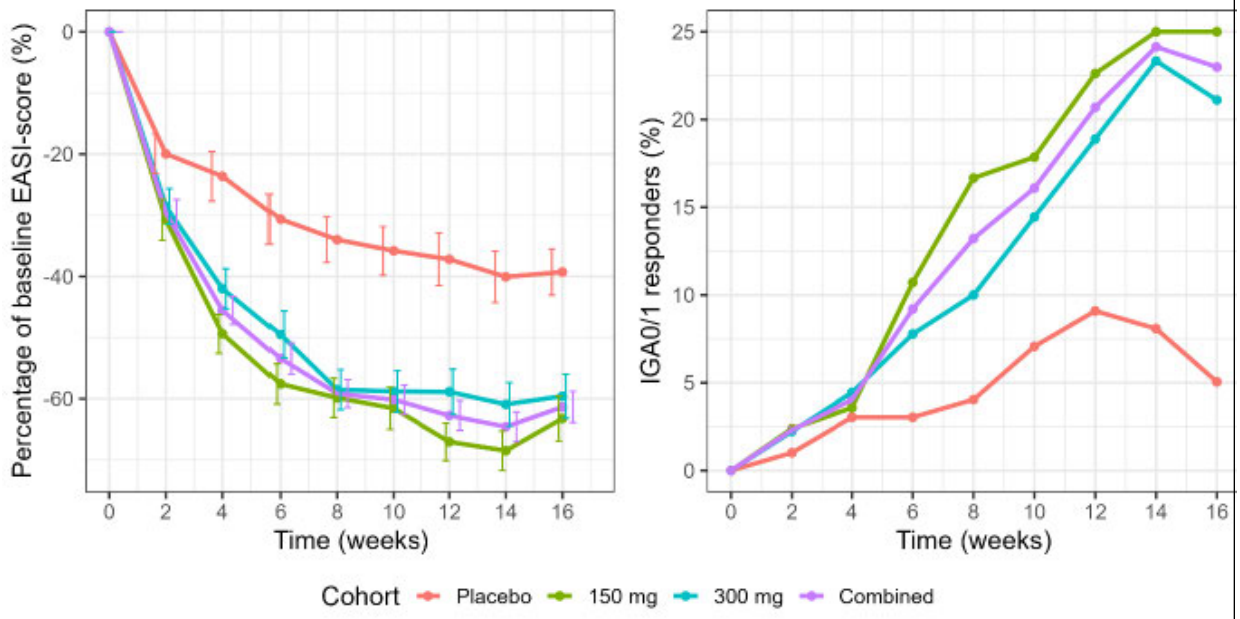
Yes. The overall Phase 3 study ECZTRA 6 efficacy results provide evidence that tralokinumab is effective for the treatment of adolescents 12 to <18 years of age with moderate-to-severe AD. The exposure-response relationships for IGA 0/1 and EASI-75 have provided supportive evidence of effectiveness.

Dose-response for efficacy in ECZTRA 6

As seen in Figure 2, subjects treated with tralokinumab had, on average, a larger reduction in EASI score than subjects treated with placebo. The reduction appeared to be slightly larger for tralokinumab 150 mg than for tralokinumab 300 mg. Even though it couldn't be concluded that there was a difference in EASI scores for tralokinumab 150 mg and 300 mg at Week 16, the reduction in EASI score was approximately 40% for placebo-treated subjects and approximately 60% for tralokinumab-treated subjects. As expected, the curve for the total tralokinumab cohort ('Combined' in Panel 2) was between the curves for the 2 tralokinumab dose cohorts.

For IGA, there was a similar trend where approximately 5% of placebo-treated subjects and 22–25% of tralokinumab-treated subjects achieved IGA response at Week 16. The response rate was marginally higher for tralokinumab 150 mg than for tralokinumab 300 mg.

Figure 2 EASI and IGA response versus time by treatment: placebo, tralokinumab 150 mg, tralokinumab 300 mg, or tralokinumab groups combined



Notes: Percent 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).

Abbreviations: EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment.

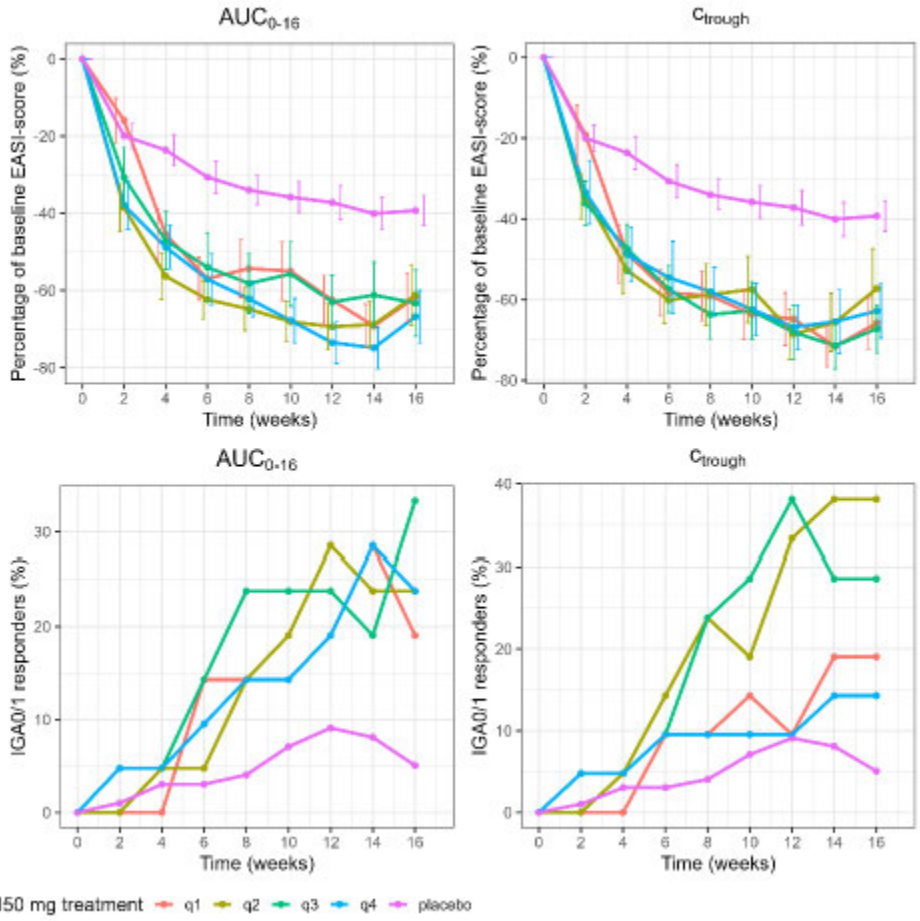
Source: Panel 2. Exposure-response analysis report (dated August 23, 2022)

Exposure-response for efficacy in ECZTRA 6

Exposure-efficacy quantile analysis

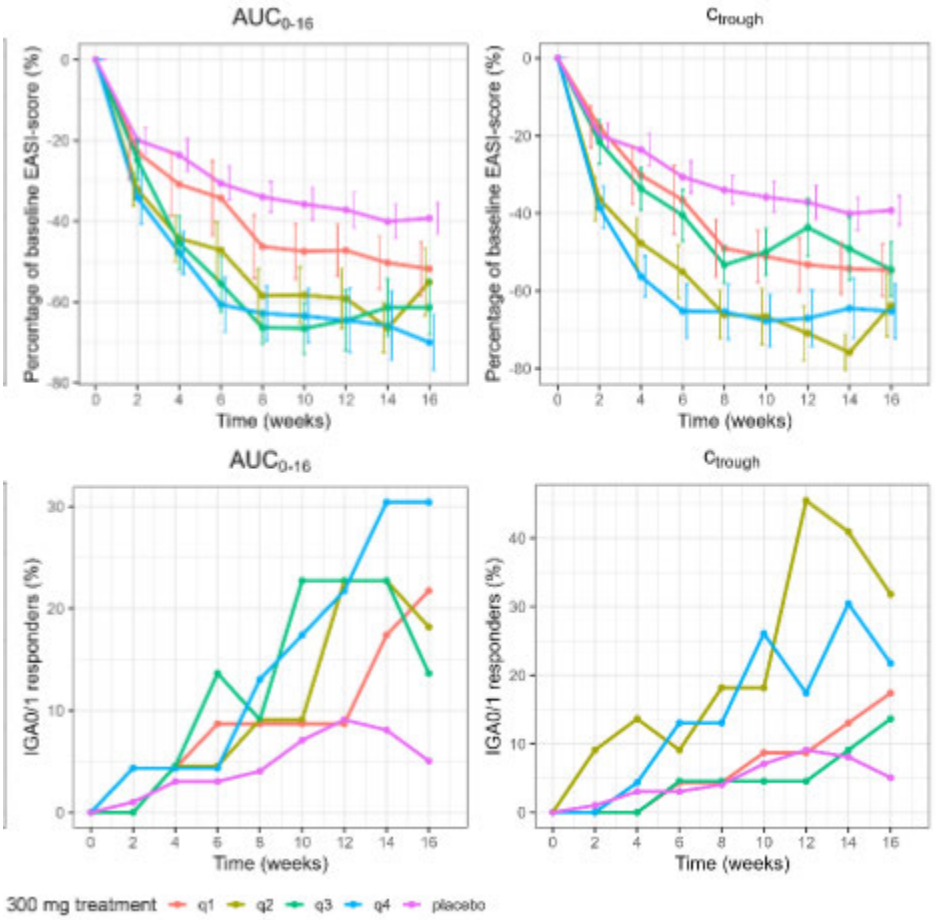
The two tralokinumab dose groups were divided into quantiles based on exposure in terms of Ctrough at Week 16 and AUC during the entire initial treatment period. The efficacy responses for the tralokinumab 150 mg, 300 mg and two doses combined quantiles are shown in Figures 3, 4 and 5.

Figure 3 EASI and IGA responses from Week 0–16 stratified by quantiles for tralokinumab 150 mg



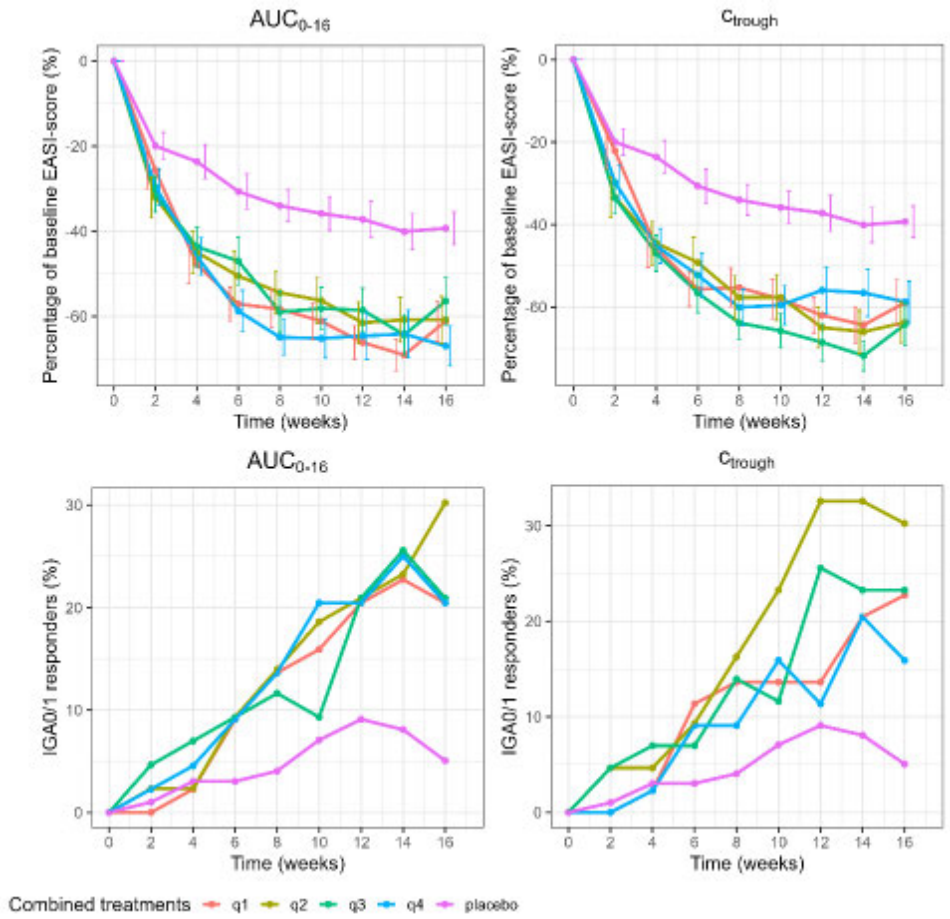
Notes: Percent change from baseline in EASI score is given as mean ± standard error of the mean; IGA 0/1 responders are defined as subjects with an IGA score of 0 (clear) or 1 (almost clear); AUC is individually predicted from Week 0–16 based on population pharmacokinetic modelling; Ctrough is the observed trough concentration at Week 16.
Abbreviations: AUC = area under the serum concentration–time curve from time zero to Week 16; Ctrough = observed trough concentration; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; Q = quantile.
Source: Panel 5. Module 5.3.4.2 Exposure–response analysis report (Dated August 23, 2022)

Figure 4 EASI and IGA responses from Week 0–16 stratified by quantiles for tralokinumab 300 mg



Notes: Percent 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 Week 0–16 based on population pharmacokinetic modelling; Ctrough is the observed trough concentration at Week 16.
Abbreviations: AUC = area under the serum concentration–time curve from time zero to Week 16; Ctrough = observed trough concentration; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; Q = quantile.
Source: Panel 7. Module 5.3.4.2 Exposure–response analysis report (Dated August 23, 2022)

Figure 5 EASI and IGA responses from Week 0–16 stratified by quantiles for tralokinumab groups combined



Notes: Percent 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 Week 0–16 based on population pharmacokinetic modelling; Ctrough is the observed trough concentration at Week 16.
Abbreviations: AUC = area under the serum concentration–time curve from time zero to Week 16; Ctrough = observed trough concentration; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; Q = quantile.
Source: Panel 7. Module 5.3.4.2 Exposure–response analysis report (Dated August 23, 2022)

Overall, in the ECZTRA 6 trial in adolescent subjects, there was a clear treatment effect for tralokinumab versus placebo with regard to reduction in EASI score from baseline to Week 16. The reduction was approximately 40% in placebo-treated subjects and approximately 60% in tralokinumab-treated subjects. There was no marked difference in the reduction in EASI score between the tralokinumab 150 mg and 300 mg dose groups and the 2 groups combined. With regard to IGA response, all results from the quantile analysis are inconclusive.

Logistic regression

The exposure metric, $AUC_{Week\ 0\text{-}16}$, was divided into 4 exposure levels:

- 0, representing the placebo group.
- [redacted] (b) (6) chosen to split the tralokinumab-treated subjects into 3 equally and sufficiently sized samples. The multi-variate logistic regression of exposure-efficacy analysis results are shown for IGA 0/1 in **Table 3** and for EASI75 in **Table 4**.

Table 3 Estimated probability of IGA 0/1 response at Week 16 by tralokinumab concentration AUC from Week 0-16

AUC week 0 to 16 (ug*day/mL)	N	N 150mg	N 300mg	Estimated probability of IGA 0/1 response	95% CI
0	94	0	0	3.41%	[1.23; 9.08%]
[redacted] (b) (6)	57	50	7	16.17%	[8.66; 28.16%]
	57	32	25	17.92%	[9.86; 30.36%]
	57	1	56	17.33%	[9.32; 29.94%]

- Logistic regression model adjusted for baseline IGA, region and AUC week 0 to 16 as factors
- Regions 'Asia' and 'Australia' were pooled to stabilize model
- IGA 0/1 response is based on the composite estimand
  Subjects who received rescue medication after Week 2 considered non-responders
  Missing values at Week 16 imputed as non-responders
- AUC is area under the tralokinumab concentration-time curve

Source: Table 1. Clinical information amendment (Dated August 26, 2022)

Table 4 Estimated probability of EASI75 response at Week 16 by tralokinumab concentration AUC from Week 0-16

AUC week 0 to 16 (ug*day/mL)	N	N 150mg	N 300mg	Estimated probability of EASI75 response	95% CI
0	94	0	0	5.50%	[2.42; 12.00%]
(b) (6)	57	50	7	25.70%	[15.89; 38.78%]
	57	32	25	26.30%	[16.32; 39.51%]
	57	1	56	30.10%	[19.22; 43.78%]

- Logistic regression model adjusted for baseline IGA, region and AUC week 0 to 16 as factors, and baseline EASI as continuous covariate
- Regions 'Asia' and 'Australia' were pooled to stabilize model
- EASI75 response is based on the composite estimand:
  Subjects who received rescue medication after Week 2 considered non-responders
  Missing values at Week 16 imputed as non-responders
- AUC is area under the tralokinumab concentration-time curve

Source: Table 2. Clinical information amendment (Dated August 26, 2022)

For the 3 tralokinumab exposure levels, the distribution of subjects across the 2 dose groups (150 mg and 300 mg) was as expected, e.g., the majority of subjects in the highest exposure group were in the highest dose group.

A clear treatment effect of the exposure to tralokinumab versus placebo was seen on both primary efficacy measures, IGA 0/1 and EASI75 (Table 3 and Table 4). For the subjects receiving tralokinumab, there was no clear correlation between the increased exposure as assessed by AUC and the tralokinumab drug response as assessed by IGA 0/1 and EASI75. For EASI75, there was a tendency towards a higher probability of response in the highest exposure group, although it must be noted that the confidence intervals are wide and overlapping.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant proposed (b) (4) (b) (4) for adolescents of 12 to <18 years of age, the Agency proposed an initial dose of 300 mg (two 150 mg injections), followed by 150 mg administered every other week due to lack of difference in the efficacy between the 150 mg and 300 mg maintenance dose.

Dose-response for efficacy in phase 3 study ECZTRA 6

In the completed randomized, double-blind, placebo-controlled, parallel-group phase 3 study ECZTRA6, tralokinumab was administered at dosages of 150 mg and 300 mg every other week during the initial treatment phase (up to Week 16) in adolescents 12 to <18 years of age with moderate-to-severe AD. Both 150 mg and 300 mg dosages appeared to perform similarly based on all primary and secondary efficacy endpoints at Week 16 and demonstrated statistical superiority to placebo based on these efficacy endpoints as shown in Table 5:

Table 5 Efficacy outcomes at Week 16 in ECTZRA 6 (adolescents) and ECZTRA 1+2 (adult monotherapy pool); full analysis set

Multiplicity-adjusted primary or secondary endpoint Additional secondary or other endpoint / *Other assessment*	ECZTRA 6			ECZTRA 1+2	
	Tralokinumab 150 mg Q2W (N=98)	Tralokinumab 300 mg Q2W (N=97)	Placebo (N=94)	Tralokinumab 300 mg Q2W (N=1192)	Placebo (N=398)
Objective assessments of AD severity and extent					
IGA 0/1 at Week 16[a]	21.4%	17.5%	4.3%	19.0%	9.0%
	17.5% (8.4 to 26.6) <0.001	13.8% (5.3 to 22.3) 0.002		9.8% (6.4 to 13.3) <0.001	
EASI75 at Week 16[a]	28.6%	27.8%	6.4%	29.0%	12.1%
	22.5% (12.4 to 32.6) <0.001	22.0% (12.0 to 32.0) <0.001		16.9% (12.8 to 20.9) <0.001	

Source: Adapted from Panel 2. Module 2.5 Clinical overview addendum (Dated November 8, 2021)

From a clinical pharmacology perspective, both 150 mg and 300 mg dosages demonstrated clear treatment effects compared to placebo from baseline to Week 16 in adolescents with moderate-to-severe AD (Tables 3 and 4, Figures 2, 3, 4 and 5). However, the 300 mg dosage did not demonstrate improved drug efficacy versus the 150 mg dose for the primary endpoints (IGA 0/1 and EASI 75).

Safety considerations

The incidence of conjunctivitis and upper respiratory tract infections does not appear to increase with increasing exposure levels. For tralokinumab 150 mg and for the combined dose group, the incidence of conjunctivitis stratified by $AUC_{Week0-16}$ was very low. For upper respiratory tract infections, the incidence was slightly higher for tralokinumab 150 mg than for placebo.

However, there was no tendency for an increase in adverse events with increasing exposure. For tralokinumab 300 mg, no events of conjunctivitis were reported. The incidence of upper respiratory tract infections was similar for tralokinumab 300 mg and placebo. As for

tralokinumab 150 mg, there was no tendency of an increase in adverse events with increasing exposure (Table 6).

Table 6 Percentage of subjects with conjunctivitis and upper respiratory tract infections in each tralokinumab dose group (150 mg, 300 mg, or combined) stratified by quantiles of exposure variables

Percentage with AE's in 150 mg treatment cohort for quantiles and placebo

	Conjunctivitis		Upper respiratory tract infections	
	AUC_{0-16} $\left[\frac{\mu g}{ml} \cdot day\right]$	C_{trough} $\left[\frac{\mu g}{ml}\right]$	AUC_{0-16} $\left[\frac{\mu g}{ml} \cdot day\right]$	C_{trough} $\left[\frac{\mu g}{ml}\right]$
Quantile	%	%	%	%
Placebo	0.0	0.0	17.2	17.2
Q1	4.8	0.0	33.3	33.3
Q2	4.8	4.8	33.3	38.1
Q3	0.0	4.8	23.8	9.5
Q4	0.0	0.0	19.0	28.6

Percentage with AE's in 300 mg treatment cohort for quantiles and placebo

	Conjunctivitis		Upper respiratory tract infections	
	AUC_{0-16} $\left[\frac{\mu g}{ml} \cdot day\right]$	C_{trough} $\left[\frac{\mu g}{ml}\right]$	AUC_{0-16} $\left[\frac{\mu g}{ml} \cdot day\right]$	C_{trough} $\left[\frac{\mu g}{ml}\right]$
Quantile	%	%	%	%
Placebo	0	0	17.2	17.2
Q1	0	0	17.4	17.4
Q2	0	0	26.1	21.7
Q3	0	0	30.4	30.4
Q4	0	0	8.7	13.0

Percentage with AE's in treatment quantiles and placebo

	Conjunctivitis		Upper respiratory tract infections	
	AUC_{0-16} $\left[\frac{\mu g}{ml} \cdot day\right]$	C_{trough} $\left[\frac{\mu g}{ml}\right]$	AUC_{0-16} $\left[\frac{\mu g}{ml} \cdot day\right]$	C_{trough} $\left[\frac{\mu g}{ml}\right]$
Quantile	%	%	%	%
Placebo	0.0	0.0	17.2	17.2
Q1	2.3	2.3	34.1	36.4
Q2	2.3	2.3	15.9	15.9
Q3	0.0	0.0	27.3	22.7
Q4	0.0	0.0	18.2	20.5

Source: Panel 10. Module 5.3.4.2 Exposure–response analysis report (Dated August 23, 2022)

Overall, the Agency proposed dosing regimen: *"For adolescents of 12 to <18 years of age, an initial dose of 300 mg (two 150 mg injections), followed by 150 mg administered every other week"* is supported by the efficacy and safety results in pivotal Phase 3 study ECZTRA 6.

Please refer to Section 8 of this Integrated Multi-Discipline Review for further information on efficacy and safety. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

An alternative dosing regimen and/or management strategy is not required for subpopulations based on intrinsic factors. Even though based on the popPK analysis, body weight was identified as a significant covariate on tralokinumab drug exposure; body weight did not result in significant efficacy difference at Week 16 between light and heavy adolescent subjects. Therefore, a dose adjustment based on body weight is not recommended for the initial treatment from weeks 0 to 16 at the dose of 150 mg Q2W following a loading dose of 300 mg in adolescents 12 to <18 years of age with moderate-to-severe atopic dermatitis (AD).

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-drug interactions are not applicable for tralokinumab as it will be administered through subcutaneous (SC) administration. Drug-drug interaction potential has been addressed in the original approval as well as through the BLA 761180 S-002.

What is the impact of immunogenicity on exposure, safety and efficacy of tralokinumab?

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

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant conducted a single Phase 3 Clinical Trial (LP0162-1334, ECZTRA 6) entitled: "*Tralokinumab monotherapy for adolescent subjects with moderate-to-severe atopic dermatitis"* to provide clinical data pertinent to the evaluation of the efficacy and safety of ADBRY for the treatment of adolescent patients with moderate to severe AD, as presented in Table 7:

Table 7 Listing of Clinical Trial Relevant to sBLA 761180-S001

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
LP0162-1334 (ECZTRA 6)	03526861	Phase 3, multicenter, randomized, double-blind, placebo-controlled Study with initial, maintenance,	Initial treatment: ADBRY 300 mg Q2W, ADBRY 150 mg Q2W, Placebo Q2W Maintenance treatment: ADBRY 300 mg Q2W or Q4W, ADBRY 150 mg Q2W or Q4W,	Primary Endpoint • IGA score of 0 (clear) or 1 (almost clear) at Week 16. Key Secondary Endpoint	Initial treatment: Weeks 0-16 Maintenance / Open-label treatments: Weeks 16-52	294 (FAS: 289)	Age 12 to 17 years Body weight ≥30 kg BSA≥ 10% EASI≥ 12 at(SC), 16 (BL)	91 sites in 10 countries (Australia, Belgium, Canada, France, Germany, Great Britain,

		and/or open-label treatment periods	Placebo Q2W Open-label treatment: ADBRY 300 mg Q2W+ optional topical corticosteroids (TCS)	• EASI75 at Week 16. Other Secondary Endpoints • Reduction ≥ 4-points in WI-NRS (weekly average) from baseline to Week 16. • Change in SCORAD from baseline to Week 16. • Change in CDLQI score from baseline to Week 16. -AEs -Presence of Anti-drug Antibodies (ADA)	Safety Follow-up: Weeks 52-66		Baseline IGA = 3 (moderate) or 4 (Severe) WI-NRS (weekly average)≥ 4	Japan, the Netherlands, Poland, and the United States

7.2. Review Strategy

Data Sources
The data sources used for the evaluation of the efficacy and safety of ADBRY included the Applicant's Clinical Overview Addendum in adolescents (M 2.5), Summary of Clinical Safety (SCS) Addendum in adolescents (M. 2.7.4), Clinical Trial Report (CTR) for LP0162-1334 (ECZTRA 6), datasets, and proposed labeling. This prior approval supplement (S-001) was submitted to BLA 761180 (SDN 64) in electronic common technical document (eCTD) format and was entirely electronic. Both Study Data Tabulation Model and analysis datasets were submitted. The analysis datasets used in this review are archived at

\\CDSESUB1\evsprod\BLA761180\0046\m5\datasets\lp0162-1334-ecztra-6

Data and Analysis Quality
A consultation for review of data fitness was obtained from CDER Office of Computational Sciences (OCS) on 2/2/2022. The OCS Jump Start team performed exploratory safety analysis and data fitness analysis for trial ECZTRA 6 for this sBLA and found the data quality acceptable. In collaboration with the OCS/Jump Start team, the Statistical and Clinical reviewers held the following meetings with the Jump Start team:

- 2/10/2022 Annotated Core DF assessment
- 2/11/2022 SDTM to ADaM traceability assessment
- 2/22/2022 Exploratory safety analysis bundles assessment

Assessments evaluated the data fitness, whether certain common analyses could be performed, and other data quality metrics including:

- Availability of appropriate variables
- Variables populated by expected data points
- Appropriate use of standard terminology
- Data well described by metadata

In general, the data submitted by the Applicant to support the efficacy and safety of ADBRY for the proposed indication appeared adequate.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial Design

The Applicant conducted a randomized, multicenter, double-blind, placebo-controlled, phase 3 trial (ECZTRA 6) to evaluate the efficacy and safety of tralokinumab monotherapy in adolescent subjects with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic therapy.

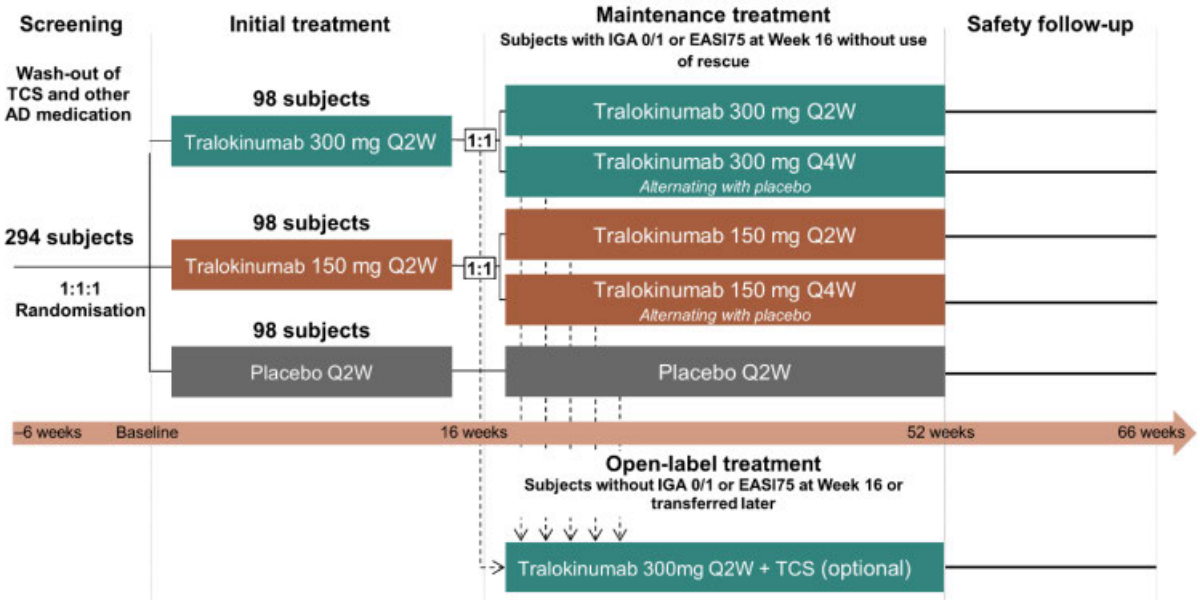
The following were the key inclusion criteria for the trial:

1. Age 12 to 17
2. Body weight at baseline ≥30.0 kg
3. Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria
4. History of AD for at least 1 year
5. History of topical corticosteroid (TCS) and/or topical calcineurin inhibitor (TCI) treatment failure or subjects for whom these topical AD treatments are medically inadvisable
6. AD involvement of ≥10% body surface area (BSA) at screening and baseline
7. An Eczema Area and Severity Index (EASI) score of ≥12 at screening and 16 at baseline; refer to Appendix 19.3 for more details on the calculations of EASI score
8. An Investigator Global Assessment (IGA) score of ≥3 at screening and at baseline; refer to Appendix 19.3 for more details on the IGA scale
9. Adolescent Pruritus numeric rating scale (NRS) average score of ≥4 during the week prior to baseline
10. Stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomization

<u>Adolescent Pruritus numeric rating scale (NRS):</u>
Subjects assessed their worst itch over the past 24 hours using an 11-point NRS ('Adolescent Pruritus NRS') with 0 indicating 'no itch' and 10 indicating 'worst itch possible'. Subjects completed the Adolescent Pruritus NRS as part of an eDiary each day in the morning from Week -2 until Week 52. Adolescent Pruritus NRS at baseline was calculated from daily assessments of worst itch during the 7 days immediately preceding randomization (Day -6 to 0). A minimum of 4 scores out of the 7 days was required to calculate the baseline average score. For subjects who did not have at least 4 scores reported during the 7 days immediately preceding the planned randomization date, randomization was postponed until this requirement was met, but without exceeding the 6 weeks' maximum duration of screening.

The trial consisted of a screening period (2-6 weeks), a 16-week initial treatment period (randomization to Week 16), a 36-week maintenance period (Weeks 16 to 52) and a 16-week off-treatment safety follow-up period (Weeks 52 to 66). Error! Not a valid bookmark self-reference. presents the trial design schematic.

Figure 6: Trial Design Schematic for ECZTRA 6



Source: Applicant's Clinical Study Report for ECZTRA 6; page 39

Initial Treatment Period (Week 0 to Week 16): the protocol specified enrolling and randomizing approximately 294 subjects from approximately 80 sites located in Europe, North America, Australia and Japan in a 1:1:1 ratio to the following treatment arms:

- Tralokinumab 300 mg every two weeks (Q2W), after a loading dose of 600 mg at baseline (N=98)
- Tralokinumab 150 mg Q2W, after a loading dose of 300 mg at baseline (N=98)
- Placebo Q2W, after a loading dose of placebo at baseline (N=98)

Randomization was stratified by region and baseline disease severity (IGA of 3 or 4). According to the protocol, to ensure blinding, all treatment arms received the same number of injections at each visit. Thus, the tralokinumab 150 mg group received both tralokinumab and placebo injections at all dosing visits.

Maintenance Treatment Period (Week 16- to Week 52): subjects achieving a 'clinical response' at Week 16 without use of rescue treatment (from Week 2 to Week 16) continued to maintenance treatment period until Week 52. Clinical response is defined as IGA of 0 or 1 (IGA 0/1) or at least 75% reduction in EASI score from baseline (EASI-75).

Subjects achieving a clinical response at Week 16 and who had been randomized to tralokinumab in the initial treatment period were re-randomized 1:1 to maintenance treatment regimens based on their initial treatment regimen and stratified by region Europe, North America, Australia, and Japan) and IGA response at Week 16.

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

- Tralokinumab 300 mg Q2W

- Tralokinumab 300 mg every 4 weeks (Q4W): alternating dose administrations of tralokinumab 300 mg or placebo.

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

- Tralokinumab 150 mg Q2W
- Tralokinumab 150 mg Q4W: alternating dose administrations of tralokinumab 150 mg (+placebo) or placebo.

Subjects randomized to placebo in the initial treatment period, who achieved a clinical response at Week 16, continued to receive placebo Q2W during the maintenance treatment period while maintaining blinding.

Open-label treatment period: (Week 16 to Week 52): subjects who did not achieve the clinical response at Week 16 and subjects who received rescue treatment from Week 2 to Week 16 were transferred to open-label treatment (tralokinumab 300 mg Q2W with optional use of TCS and/or TCI) at Week 16, if considered appropriate by the investigator. In addition, subjects were transferred from maintenance treatment to open-label treatment if they met any of the criteria listed below and transfer to open-label treatment was considered appropriate by the investigator.

Subjects with IGA=0 at Week 16:

- IGA of at least 2 and not achieving EASI-75 over at least a 4-week period (i.e., over 3 consecutive visits)

Subjects with IGA=1 at Week 16:

- IGA of at least 3 and not achieving EASI-75 over at least a 4-week period (i.e., over 3 consecutive visits).

Subjects with IGA >1 at Week 16:

- Not achieving EASI-75 over at least a 4-week period (i.e., over 3 consecutive visits).

Subjects who received rescue treatment during the maintenance treatment period should be transferred to open-label treatment. Subjects who were transferred to open-label treatment continued their scheduled visit sequence up to Week 52.

Safety follow-up period (Week 52 to Week 66): after completion of the treatment periods or premature discontinuation of study medication, all subjects should enter a 14-week off-treatment follow-up period for the assessment of safety, PK, and immunogenicity, except subjects who were transferred to the long-term extension trial ECZTEND before Week 66 (see below). During follow-up, subjects were allowed to receive standard of AD care (excluding biologic therapies) at the Investigator's discretion, if needed.

Long-term extension trial (ECZTEND): eligible subjects from selected countries were invited to enter a long-term extension trial conducted under a separate protocol (ECZTEND). Subjects who transferred to ECZTEND, were required to have had their last visit in the treatment period (Week 52) under the current protocol (ECZTRA 6). Subjects could enter ECZTEND up to 26 weeks from

their last investigational medicinal product (IMP) injection in the present trial (Week 50) to their first IMP injection in ECZTEND (baseline). Subjects could therefore enter ECZTEND (baseline) without completing the safety follow-up visit (16 weeks after their last IMP injection) in the present trial, and those subjects would have their safety follow-up visit in ECZTEND.

8.1.2. Endpoints

The protocol specified the following co-primary endpoints:

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

The protocol listed the following secondary endpoints:

- Change in Scoring Atopic Dermatitis (SCORAD) from baseline to Week 16
- Reduction in Adolescent Pruritus NRS (weekly average) of at least 4 from baseline to Week 16
- Change in Children's Dermatology Life Quality Index (CDLQI) score from baseline to Week 16

The Agency noted in the advice letter dated 10/8/2021 that since IGA 0/1 and EASI-75 at Week 16 are sequentially tested in the order listed above, the IGA 0/1 is considered as the primary endpoint and EASI-75 as a key secondary endpoint.

Furthermore, the Agency noted in the advice letters dated 10/24/2018, 3/29/2019 and 10/8/2021 that the secondary endpoints of change from baseline in Scoring Atopic Dermatitis (SCORAD) score and change in Dermatology Life Quality Index (DLQI) score may not translate into clinically meaningful treatment effects, and therefore, should be excluded from the multiplicity testing procedure. Therefore, endpoints based on CDLQI and SCORAD are not presented in this review.

The protocol also listed several 'additional secondary endpoints' and 'other secondary endpoints'; however, such endpoints are not included in the multiplicity testing strategy, and therefore, are not presented in this review.

<u>Scoring Atopic Dermatitis:</u>
According to the protocol, SCORAD is a validated tool to evaluate the extent and severity of AD lesions, along with subjective symptoms. The assessment consists of 3 components: extent, intensity and subject symptom. The maximum total score is 103, with higher values indicating more severe disease.

8.1.3. Statistical Methodologies

Analysis Populations:
The protocol for ECZTRA 6 specified conducting efficacy analyses using the full analysis set (FAS), defined as all subjects randomized to initial treatment.

The protocol also specified conducting supportive analyses using the per-protocol set (PPS), defined to exclude subjects from the FAS for whom any of the following conditions apply:

- Receive no treatment with the investigational medicinal product (IMP)
- Provide no assessment of IGA or EASI following start of treatment
- Are known to have taken the wrong IMP throughout the initial treatment period
- Do not fulfill the inclusion criteria #3, 6, 7, and 8, as listed in Section Error! Reference source not found. of this review

The protocol also defined a maintenance analysis set (MAS) as subjects in the full analysis set who receive maintenance treatment at Week 16.

The SAP introduced the following modifications to the analysis sets:

- "At sites 340 (n=2) and 341 (n=7) several critical GCP non-compliance issues have been identified. At site 340 the validity of key eligibility criteria (e.g., AD diagnosis and disease severity) for the 2 subjects has been questioned. Site 341 was closed due to findings in other ECZTRA trials where e.g., the AD diagnosis, exposure to IMP and safety collection were questioned. In ECZTRA 6, similar findings have been detected. It cannot be confirmed that subjects from sites 340 and 341 do represent the targeted population of adolescents with moderate-to-severe AD. Therefore, subjects from the two sites will be excluded from the analyses sets and will be reported separately in listings and tables, as appropriate."
- "All subjects randomized to initial treatment who were exposed to IMP and not being from sites 340 and 341 are included in the full analysis set (FAS) and will be analyzed for efficacy up to Week 16. For subjects not exposed to IMP, the decision to withdraw cannot be biased by knowledge of the assigned treatment due to the blinding. This definition of the FAS implements the consideration mentioned in the protocol regarding exclusion of randomized subjects per ICH E9, Section 5.2.1."
- "The safety analysis set comprises all subjects randomized to initial treatment who were exposed to IMP and not being from sites 340 and 341. The protocol further specifies to exclude subjects from the safety analysis set for whom no post-baseline safety data are available. However, since all subjects receive the first dose of IMP in connection with the Week 0 visit and are subsequently monitored for immediate drug reactions, all exposed subjects are considered to have post-baseline safety data available and no such further exclusions will be made."
- "Subjects who are not exposed to maintenance treatment and subjects from sites 340 and 341 will be excluded from the maintenance analysis set. This follows the same

principle that leads to exclusion of unexposed subjects from the full analysis set and is in alignment with ICH E9."

Estimands:

The following three estimands were defined in the protocol/SAP for the analysis of the primary endpoints to incorporate two main types of intercurrent: 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 from Week 2 to Week 16, 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 used from Week 2 to 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 secondary endpoints:

The protocol/SAP specified analyzing the primary endpoints (i.e., IGA 0/1 and EASI-75) using the Cochran-Mantel-Haenszel (CMH) test stratified by region (Europe and North America, Japan, and Europe) and baseline disease severity (IGA of 3, 4) for the difference in response rates between treatment groups for all three estimands. Analyses for the primary and tertiary estimands will be based on the full analysis set. For the analysis of the secondary estimand, the SAP states that "data collected after permanent discontinuation of IMP or after initiation of rescue medication will not be applied". The analysis of the primary estimand was also repeated using the PPS.

The protocol/SAP specified analyzing the binary secondary endpoint (i.e., proportion of subjects with reduction of Adolescent Pruritus NRS weekly average of at least 4 from baseline to Week 16) using the same method as for the analysis of the primary endpoints using all three estimands. The analyses are based on subjects in the FAS with a baseline Adolescent Pruritus NRS weekly average of at least 4. According to the SAP, the weekly average is calculated if at least 4 assessments are available.

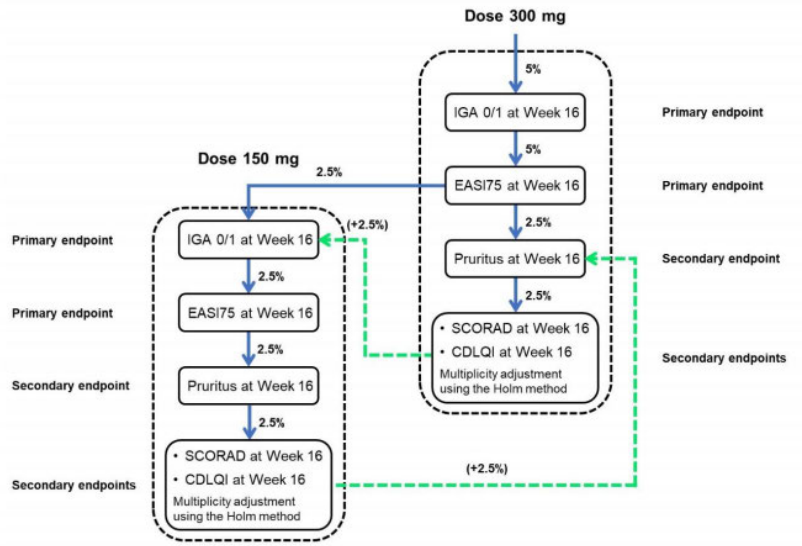
The protocol specified analyzing the continuous secondary endpoints (i.e., change from baseline to Week 16 in SCORAD and CDLQI) using a repeated measurements model on the post baseline responses up to Week 16 with an unstructured covariance matrix.

Multiplicity Testing Procedure (MTP):

The protocol specified the multiplicity testing procedure (MTP) outlined in Figure 7 Multiplicity Testing Procedure (US Submission)
to control the overall Type 1 error rate for the primary analyses of the primary estimand for primary and secondary endpoints.

The two co-primary endpoints for the tralokinumab 300 mg dose are first tested hierarchically at an overall 5% significance level, after which the significance level is split evenly between testing of the primary endpoints for the tralokinumab 150 mg dose and testing of the secondary endpoint Pruritus at Week 16 for the tralokinumab 300 mg dose. If all the hypotheses of no difference to placebo for the tralokinumab 300 mg dose are rejected, then the 2.5% significance level is passed on to the testing of all the endpoints for the tralokinumab 150 mg dose. Similarly, if the hypotheses of no difference to placebo for all the endpoints of the tralokinumab 150 mg dose are rejected, the 2.5% significance level is passed on to the testing of all secondary endpoints for the tralokinumab 300 mg dose.

Figure 7 Multiplicity Testing Procedure (US Submission)



Note: To protect the family-wise type I error. The numbers in parentheses indicate significance levels that have been passed on from rejected hypotheses for the other tralokinumab dose level.
Source: Applicant's Protocol for ECZTRA 6, Version 7; page 112

Maintenance analyses:
According to the SAP, the maintenance of effect of tralokinumab is evaluated at Week 52 for subjects who achieved clinical response at Week 16 without rescue medication. Subjects who receive rescue treatment between Week 16 and Week 52 are considered non-responders. Missing data for subjects who did not attend the Week 52 visit and who did not use rescue treatment between Week 16 and Week 52, are also imputed as non-responders. Additional analysis disregarding use of rescue will be performed (treatment policy approach).

Methods for handling the missing data:
Table 8 summarizes the protocol/SAP-specified methods for handling the missing data in the analysis of the primary and binary secondary endpoints.

For the maintenance effect, all subjects who prior to Week 52 received rescue medication, and/or were transferred to the open-label arm were considered non-responders. In addition, all

subjects with missing maintenance endpoint data at Week 52 visit were also imputed as non-responders. 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 adverse event or lack of efficacy were imputed using last observation carried forward (LOCF).

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Table 8: 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 are considered non-responders; Subjects who did not attend the Week 16 visit and did not receive rescue medication prior to Week 16 are also considered non-responders)	"Sensitivity Analysis 1": All subjects who have permanently discontinued IMP prior to Week 16 are imputed as non-responders, even if no rescue medication had been used.
		"Sensitivity analysis 2": Subjects who have withdrawn due to an adverse event or due to lack of efficacy are still considered non-responders. Data missing for other reasons str imputed using LOCF.
		"Sensitivity analysis 3": A tipping point analysis using MI: Subjects who prior to the Week 16 visit had received rescue medication are considered non-responders. Subjects in the tralokinumab arms with missing Week 16 data are considered non-responders, while missing Week 16 data for subjects in the placebo arm who did not use rescue medication from Week 2 to Week 16 are imputed from a Bernoulli distribution with parameter p (ranging from 0 to 1). By varying the parameter p, different percentages of placebo subjects are assumed to be responders. For each of the active treatment groups, the tipping point is calculated as the smallest placebo response rate where the p-value exceeds the nominal significance level alpha. If all p-values are below alpha, tipping point is coded as "Not reached". If the original analysis (i.e., p=0 corresponds to primary analysis for primary estimand) already does not reach nominal significance, the tipping point is coded as "Not applicable". A tipping-point above 0.05 for IGA 0/1 and Adolescent Pruritus NRS ≥ 4 and above 0.10 for EASI-75 is not considered clinically plausible. The MI procedure includes the following steps for each value of *p*: 100 copies of the dataset are generated (seed=11109934) 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 IGA values using ordinal logistic regression model with region and baseline disease severity as factors. (100 datasets; seed=11109934). In each group, intermittent missing values were imputed using LOCF to obtain a monotone missing data pattern. • EASI-75 and Adolescent Pruritus NRS: MI of the underlying EASI/NRS values, using ANCOVA model with effects of baseline value as a covariate, and region and baseline disease severity as factors (100 datasets; seed=11109934). Intermittent missing values were imputed in each group using MCMC method (100 datasets; seed = 29099734).	MI for missing data at Week 16 using a pattern mixture model, where missing data in the tralokinumab arms as well as the placebo arm are imputed from observed data in the placebo arm ("using a so-called copy-reference approach"). The protocol 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 6 groups, defined according to randomized treatment arm and whether or not subjects have permanently discontinued IMP prior to Week 16.	NRI

Abbreviations: Abbreviations: ANCOVA, analysis of Covariance; IMP, investigational medicinal product; LOCF, last observations carried forward; MAR, missing at random; MCMC, Markov Chain Monte Carlo; MI, Multiple imputation; NRS, numeric rating scale; WOCF, Worst observation carried forward
Source: Reviewer's table; excerpts from the Applicant's protocol and SAP for ECZTRA 3.

Statistical Impacts Due to COVID-19 pandemic:
An urgent safety measure was implemented during the trial which allowed for collection of adverse events by phone if trial visits at site were not possible due to local preventive measures during the COVID-19 pandemic. According to the Applicant, data collection in the initial treatment period was not affected by the COVID-19 pandemic due to the timing (all subjects passed Week 16 when the pandemic started), while the impact in the maintenance and open-label treatment periods as well as safety follow-up period is considered limited. In the context of efficacy analyses, the SAP specified conducting sensitivity analysis of response at Week 52 using LOCF imputation for subjects missing assessments at Week 52 due to COVID-19 pandemic instead of imputing data as non-responders.

8.1.4. Subject Disposition, Demographics, and Baseline Disease Characteristics

ECZTRA 6 enrolled and randomized a total of 301 subjects; however, 9 of the randomized subjects were enrolled in sites 340 and 341 and 3 of the randomized subjects (one in each arm) were not dosed. Therefore, a total of 12 subjects were excluded for the FAS. Table 9 presents the disposition of subjects during the initial treatment period (first 16 weeks) for ECZTRA 6. The discontinuation rate was slightly higher in placebo arm compared to the active arms. The most common reason for discontinuation was 'withdrawal by parent/guardian'.

Table 9: Disposition of Subjects through Week 16 - ECZTRA 6 (FAS[1])

	Tralokinumab		
Subject Disposition	**300 mg Q2W (N=97)**	**150 mg Q2W (N=98)**	**Placebo (N=94)**
Discontinued before Week 16	3 (3%)	5 (5%)	8 (9%)
Reason for Discontinuation			
Adverse Event	0 (0%)	2 (2%)	0 (0%)
Lack of Efficacy	0 (0%)	0 (0%)	1 (1%)
Lost to Follow-up	0 (0%)	0 (0%)	2 (2%)
Withdrawal by Parent/Guardian	2 (2%)	1 (1%)	3 (3%)
Withdrawal by Subject	0 (0%)	2 (2%)	0 (0%)
Other	1 (1%)	0 (0%)	2 (2%)
Completed Week 16 on Treatment[2]	94 (94%)	93 (95%)	86 (91%)
Assigned to Maintenance Treatment	24 (24%)	26 (26%)	6 (6%)
Transferred to Open-Label Treatment	65 (65%)	70 (69%)	79 (79%)
Discontinued at Week 16	0 (0%)	2 (2%)	1 (1%)

Source: Statistical Reviewer's Analysis (same as Applicant's analysis); ADSL.xpt
[1] Full Analysis Set (FAS) was defined as all randomized subjects who were dosed with sites 340 and 341 removed.
[2] I.e., no permanent discontinuation of IMP before Week 16
Abbreviations: FAS; full analysis set; Q2W, every two weeks

Demographics and baseline disease characteristics for ECZTRA 6 are presented in Table 10. Demographics were generally balanced across the treatment arms. The majority of the subjects were White (approximately 70%). The mean age was approximately 38 years old. The baseline disease characteristics were generally balanced across the treatment arms. In general,

approximate equal proportion of subjects were enrolled in the trial with IGA score of 3 (moderate) and IGA score of 4 (severe).

Table 10: Demographics - Trial ECZTRA 6 (FAS[1])

	Tralokinumab		
	300 Q2W (N=97)	**150 Q2W (N=98)**	**Placebo (N=94)**
Age (years)			
Mean (SD)	14.6 (1.7)	14.8 (1.7)	14.3 (1.6)
Median	15	15	14
Range	12, 17	12, 17	12, 17
Age Group, n (%)			
12-14	45 (46)	37 (38)	49 (52)
15-17	52 (54)	61 (62)	45 (48)
Sex, n (%)			
Female	50 (52)	47 (48)	43 (46)
Male	47 (48)	51 (52)	51 (54)
Race, n (%)			
White	56 (58)	55 (56)	53 (56)
American Indian or Alaska Native	0 (0)	2 (2)	1 (1)
Asian	20 (21)	28 (29)	23 (24)
Black or African American	14 (14)	7 (7)	11 (12)
Native Hawaiian or Other Pacific Islander	2 (2)	0 (0)	2 (2)
Missing	5 (5)	6 (6)	4 (4)
Region, n (%)			
Asia	11 (12)	10 (10)	11 (11)
Australia	4 (4)	5 (5)	5 (5)
Europe	32 (34)	33 (34)	33 (34)
North America	47 (50)	50 (51)	48 (49)
Baseline IGA, n (%)			
3	49 (51)	54 (55)	51 (54)
4	48 (49)	44 (45)	43 (46)
EASI			
Mean (SD)	31.8 (13.9)	32.1 (12.9)	31.2 (14.5)
Median	28.0	28.9	27.2
Range	16 – 72	16 – 68.4	16 – 68.4
Adolescent Pruritus NRS			
Mean (SD)	7.8 (1.5)	7.5 (1.6)	7.5 (1.7)
Median	8.1	7.5	7.6
Range	4.1 – 10	1.4 – 10	2.1 – 10
>=4, n (%)	96 (99)	95 (97)	90 (96)
Baseline BSA			
Mean (SD)	49.6 (23.3)	52.4 (22.6)	51.4 (23.9)
Median	44	49	52
Range	16, 100	11, 100	10, 100
Prior Use of Systemic Immunosuppressant			
Yes	19 (20)	22 (22)	20 (21)[2]
No	78 (80)	76 (78)	73 (78)

Source: Statistical Reviewer's Analysis (same as Applicant's analysis); ADSL.xpt, ADEASI.xpt, ADEDIARY.xpt

[1] Full Analysis Set (FAS) was defined as all randomized subjects who were dosed with sites 340 and 341 removed.

[2] Unknown use of prior systemic Immunosuppressant for 1 subject

Abbreviations: FAS; full analysis set; SD, standard deviation; Q2W, every two weeks

8.1.5. Use of Rescue Medication

The use of rescue medication during the initial period is summarized by treatment arm in Table 11. The use of rescue medication during the initial treatment period was similar across the two active arms and higher in the placebo arm. As noted in Section 8.1.3 subjects who initiated rescue medication from Week 2 to Week 16 were considered non-responders for the primary ('composite') estimand. We note that only a few subjects (9 subjects; 2 subjects in each active arm and 5 in the placebo arm) initiated rescue treatment by Week 2 and did not continue on rescue medication later on.

Table 11: Rescue Medication During Initial Treatment Period (FAS[1]) – ECZTRA 6

	Tralokinumab		
	300 mg Q2W (N=97)	**150 mg Q2W (N=98)**	**Placebo (N=94)**
Any rescue medication	29 (30%)	33 (34%)	53 (56%)

Source: Statistical Reviewer's Analysis (same as Applicant's analysis); ADSL.xpt
[1] Full Analysis Set (FAS) was defined as all randomized subjects who were dosed with sites 340 and 341 removed.
Abbreviations: FAS; full analysis set; Q2W, every two weeks

8.1.6. Results for the Primary and Secondary Efficacy Endpoints

Table 12 presents the results for the primary and secondary efficacy endpoints at Week 16 for ECZTRA 6. Both tralokinumab doses were statistically superior to placebo for the primary endpoint of IGA success at Week 16, as well as for the secondary endpoints of EASI-75 and reduction of Adolescent Worst Pruritus NRS of ≥4 at Week 16. The two tralokinumab doses (150 mg and 300 mg) seem to perform similarly based on these three endpoints, with slightly higher IGA 0/1 response rate for the 150 mg compared to the 300 mg.

As noted in Section 8.1.3, the Applicant stated that due to several GCP non-compliance issues identified at sites 340 (n=2) and 341 (n=7), it cannot be confirmed that subjects from these sites do represent the targeted population of adolescents with moderate-to-severe AD. Therefore, the SAP modified the primary analysis population (referred to as full analysis set) to exclude subjects from sites 340 and 341. The results with the two subjects enrolled in sites 340 and 341 included in the analysis (see
Table 51 Results for the Primary and Secondary Endpoints at Week 16 - ECZTRA 6 (RSS; Primary Analysis; Primary Estimand1) of Appendix 19.3) are similar to those in Table 12. The results in the PP population (not shown here) were similar to those in the FAS population.

Table 12: Results for the Primary and Secondary Endpoints at Week 16 - ECZTRA 6 (FAS; Primary Analysis; Primary Estimand[1])

	Tralokinumab		
Endpoint	**300 mg Q2W (N=97)**	**150 mg Q2W (N=98)**	**Placebo (N=94)**
IGA 0/1 (Primary)	17 (17.5%)	21 (21.4%)	4 (4.3%)
Difference from Placebo (95% CI)	13.8% (5.3%, 22.3%)	17.5% (8.4%, 26.6%)	-
P-Value	0.002	<0.001	-

EASI-75	27 (27.8%)	28 (28.6%)	6 (6.4%)
Difference from Placebo (95% CI)	22.0% (12.0%, 32.0%)	22.5% (12.4%, 32.6%)	-
P-Value	<0.001	<0.001	-
Reduction of Adolescent Worst Pruritus NRS of ≥4[2]	24/96 (25.0%)	22/95 (23.2%)	3/90 (3.3%)
Difference from Placebo (95% CI)	21.7% (12.3%, 31.1%)	19.9% (10.6%, 29.2%)	-
P-Value	<0.001	<0.001	-

Source: Statistical Reviewer's Analysis (same as Applicant's analysis); ADIGA.xpt, ADEASI.xpt, ADEDIARY.xpt
[1] Full Analysis Set (FAS) was defined as all randomized subjects who were dosed with sites 340 and 341 removed. Subjects who received rescue medication considered non-responders; Subjects with missing data at Week 16 imputed as non-responders
[2] Reduction of Adolescent Worst Daily Pruritus Numeric Rating Scale (NRS) score (weekly average) ≥4 from baseline to Week 16, among subjects with baseline score of ≥4
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; 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
Note: Difference, 95% CI, and p-value are based on CMH test stratified by region and baseline IGA score.

Table 13 presents the number of subjects with missing data for the primary efficacy endpoint by week and treatment arm during the initial period. Overall, the proportion of subjects with missing data was relatively low. At Week 16, the missing data rate was slightly higher in the tralokinumab 150 mg and placebo groups compared to the tralokinumab 300 mg group.

Table 13: Missing Data for the Primary Efficacy Endpoint by Week During the Initial Period - ECZTRA 6 (FAS[1])

	Tralokinumab		
Week	**300 mg Q2W (N=97)**	**150 mg Q2W (N=98)**	**Placebo (N=94)**
Week 2	1 (1%)	0 (0%)	1 (1%)
Week 4	1 (1%)	2 (4%)	4 (4%)
Week 6	3 (3%)	3 (3%)	3 (3%)
Week 8	2 (2%)	3 (3%)	6 (6%)
Week 10	4 (4%)	5 (5%)	8 (9%)
Week 12	4 (4%)	9 (9%)	4 (4%)
Week 14	2 (2%)	6 (6%)	11 (12%)
Week 16	2 (2%)	6 (6%)	7 (7%)

Source: Statistical Reviewer's Analysis (same as Applicant's analysis); ADIGA.xpt
[1] Full Analysis Set (FAS) was defined as all randomized subjects who were dosed with sites 340 and 341 removed.
Abbreviations: FAS; full analysis set; Q2W, every two weeks

The protocols specified primary and sensitivity analyses for the handling of missing data for all three different estimands for the binary efficacy endpoints, as summarized in Table 8 of this review. The results for the primary and secondary efficacy endpoints by the various imputation methods for each estimand are presented in Appendix 19.3 (see Table 52 Comparison of Different Approaches for Handling Missing Data – ECZTRA 6 (FAS*)). The primary analysis for the tertiary estimand defined in the SAP and protocol could not be performed as insufficient data were available from subjects who discontinued IMP to support multiple imputation of missing values within the treatment groups. The results for all endpoints in consideration were similar across the primary analysis and the sensitivity analyses for each estimand.

A noted in Section 8.1.3 (see Table 8), a tipping point analysis using multiple imputation was specified as a third sensitivity analysis of the primary estimand. For the tipping point analyses of

the IGA 0/1 at Week 16, the tipping point was reached at high imputation response rates in the placebo group (87%) when testing tralokinumab 300 mg Q2W vs. placebo, which was considered clinically implausible, and was not reached when testing tralokinumab 150 mg Q2W vs. placebo. For the tipping point analyses of EASI-75, the tipping point was not reached for any of the tests of tralokinumab 300 mg Q2W vs. placebo and tralokinumab 150 mg Q2W vs. placebo.

IGA 0/1 at Week 16:
The primary and sensitivity analyses of the secondary estimand ('hypothetical') led to higher response rates, particularly in the placebo arm which resulted in lower (and non-significant) treatment difference to placebo compared with the results for the primary estimand. The reader is reminded that data collected after permanent discontinuation of IMP or initiation of rescue medication were excluded from the secondary estimand.

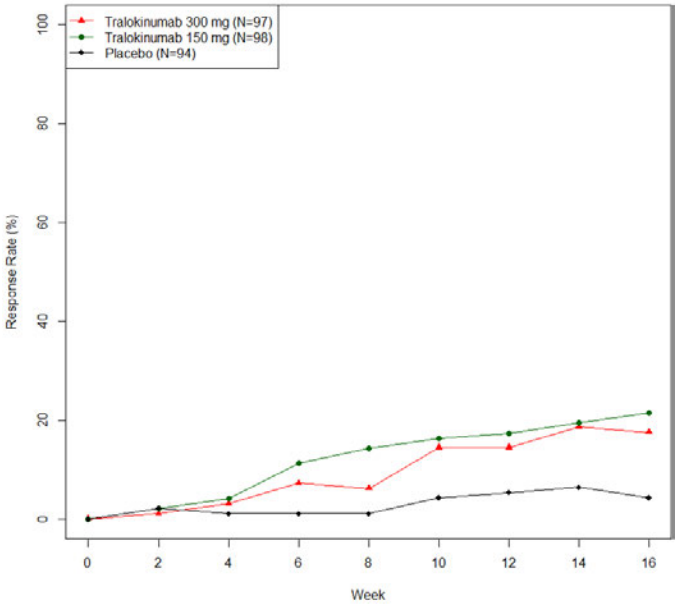
EASI-75 and Worst Daily Pruritus NRS at Week 16:
For the secondary and tertiary estimands, the response rates were higher within each treatment group compared with the primary estimand; however, the treatment differences were comparable across estimands.

8.1.7. Efficacy Over Time

8.1.7.1. Initial Treatment Period

For the initial treatment period, subjects were evaluated for the IGA scores at baseline and Weeks 2, 4, 6, 8, 10, 12, and 16. Figure 8: IGA Success (IGA 0/1) for the Initial Treatment Period for Trial ECZTRA 6 (FAS; NRI1) presents the IGA response (IGA of 0/1) rates over time for ECZTRA 6.

Figure 8: IGA Success (IGA 0/1) for the Initial Treatment Period for Trial ECZTRA 6 (FAS; NRI1)



Source: Statistical Reviewer's Analysis
[1] Full Analysis Set (FAS) was defined as all randomized subjects who were dosed with sites 340 and 341 removed; Subjects who received rescue medication considered non-responders; Subjects with missing data at Week 16 imputed as non-responders
Abbreviations: FAS, full analysis set; IGA, Investigator's Global Assessment

8.1.7.2. Maintenance Period

Subjects achieving a clinical response (IGA 0/1 or EASI 75) at Week 16 without use of rescue treatment (from Week 2 to Week 16) continued to maintenance treatment period until Week 52. A total of 56 subjects in the FAS were assigned to maintenance treatment period as indicated in Table 9. None of the subjects who were assigned to maintenance treatment had prior use of rescue medication and all these subjects were dosed with maintenance treatment

Among the 97 subjects originally randomized to the tralokinumab 300 Q2W arm, only 24 subjects were re-randomized in a 1:1 ratio to tralokinumab 300 Q2W or tralokinumab 300 Q4W. Among the 98 subjects originally randomized to the tralokinumab 150 Q2W arm, only 26 subjects were re-randomized in a 1:1 ratio to tralokinumab 150 Q2W or tralokinumab 150 Q4W. All randomized subjects in the maintenance treatment period were dosed. One subject originally randomized to tralokinumab 150 Q2W arm was incorrectly considered to have achieved a clinical response at Week 16, and therefore, was incorrectly assigned to maintenance treatment.

Table 14 presents the proportion of Week 16 responders (IGA 0/1 and EASI 75) who maintained their response at Week 52 of the maintenance period. However, the reviewer notes that only a very small number of Week 16 responders were transferred to the maintenance period, to allow any meaningful conclusions regarding the maintenance of response.

Table 14: Maintenance of Response at Week 52 – ECZTRA 6 (MAS; NRI[1])

	Tralokinumab

Endpoint	300 mg Q2W/Q2W (N=11)	300 mg Q2W/Q4W (N=13)	150 mg Q2W/Q2W (N=12)	150 mg Q2W/Q4W (N=14)
IGA 0/1 among Week 16 IGA 0/1 responders	3/8 (38%)	7/8 (88%)	6/9 (67%)	6/10 (60%)
EASI 75 among Week 16 EASI 75 responders	3/6 (50%)	7/8 (88%)	6/9 (67%)	6/10 (60%)

Source: Statistical Reviewer's Analysis
[1] Maintenance Analysis Set (MAS) defined as subjects in the full analysis set who receive maintenance treatment at Week 16. Subjects who received rescue medication or were transferred to open-label treatment were considered non-responders. Missing data at Week 52 (including missing data due to COVID-19) were imputed using the non-responder imputation (NRI) method.
Abbreviations: FAS, full analysis set; CI, Confidence Interval; LOCF, last observation carried forward; IMP, investigational medicinal product; NRS, numeric rating scale; Q2W, every 2 weeks
Note: Difference, 95% CI and p-value are based on the CMH test stratified by region and baseline IGA score

8.1.8. Additional Analyses

This section summarizes 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 co-primary endpoints. EASI 90 was pre-specified as an "additional secondary endpoint", which was not included in the multiple testing procedure. Therefore, the results for such endpoint are viewed as exploratory for this review.

Table 15: Results for EASI 90 at Week 16 - ECZTRA 6 (FAS; Primary Analysis; Primary Estimand[1])

	Tralokinumab		
Endpoint	**300 mg Q2W (N=97)**	**150 mg Q2W (N=98)**	**Placebo (N=94)**
EASI 90	17 (17.5%)	19 (19.4%)	4 (4.3%)
Difference from Placebo (95% CI)	13.7% (5.2%, 22.2%)	15.3% (6.5%, 24.1%)	-
P-Value	<0.001	<0.001	-

Source: Statistical Reviewer's Analysis (same as Applicant's analysis); ADIGA.xpt, ADEASI.xpt, ADEDIARY.xpt
[1] Full Analysis Set (FAS) was defined as all randomized subjects who were dosed with sites 340 and 341 removed. Subjects who received rescue medication considered non-responders; Subjects with missing data at Week 16 imputed as non-responders
Abbreviations: CI, Confidence Interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; IMP, investigational medicinal product; NRS, numeric rating scale; Q2W, every 2 weeks

8.1.9. Findings in Special/Subgroup Populations

8.1.9.1. Sex, Race, Age, and Baseline Disease Severity

The results for IGA success at Week 16 by sex, race, and baseline IGA score for ECZTRA 6 are presented in Table 16. The results for EASI 75 at Week 16 by these same subgroups for ECZTRA 6 are presented in Table 17.

The sample size in the subgroups based on race (except for White) are small; therefore, it would be difficult to detect any differences in efficacy between these subgroups and their complements.

A smaller IGA 0/1 treatment effect was observed in subjects with a baseline IGA score of 4 (severe) compared to baseline IGA score of 3 (moderate) for both tralokinumab doses, mainly attributed to the response rates for the active treatment arms. A smaller EASI-75 treatment effect was also observed for the tralokinumab 150 mg dose in subjects with a baseline IGA score of 4 (severe) compared to baseline IGA score of 3 (moderate); however, the treatment effect for EASI-75 was consistent for the tralokinumab 300 mg dose.

Table 16: IGA 0/1 Response at Week 16 by Age, Sex, Race and Baseline IGA Score - ECZTRA 6 (FAS; Primary Analysis; Primary Estimand[1])

Subgroups (n[Tral 300 mg], n[Tral 150 mg], n[P])	Tralokinumab 300 mg Q2W (N=97)	Tralokinumab 150 mg Q2W (N=98)	Placebo (N=94)	Difference from Placebo (95% CI) 300 mg Q2W	Difference from Placebo (95% CI) 150 mg Q2W
Sex					
Male (47, 51, 51)	11%	26%	2%	9% (-1%, 18%)	24% (11%, 36%)
Female (50, 47, 43)	24%	17%	7%	17% (3%, 31%)	10% (-3%, 23%)
Race					
White (46, 55, 53)	21%	20%	6%	16% (3%, 28%)	14% (2%, 27%)
Black or African Americans (14, 7, 11)	21%	0%	9%	12% (-15%, 40%)	-9% (-26%, 8%)
Asian (20, 28, 23)	10%	25%	0%	10% (-3%, 23%)	25% (9%, 41%)
Other (2, 2, 3)	0%	0%	0%	-	-
Missing (5, 6, 4)	0%	50%	0%	-	50% (10%, 90%)
Baseline IGA					
Moderate (49, 54,51)	24%	31%	6%	19% (5%, 32%)	26% (12%, 40%)
Severe (48, 44, 43)	10%	9%	2%	8% (-2%, 18%)	7% (-3%, 16%)
Overall	**18%**	**21%**	**4%**	**13% (5%, 22%)**	**17% (8%, 26%)**

Table 17: EASI-75 Response at Week 16 by Age, Sex, Race and Baseline IGA Score - ECZTRA 6 (FAS; Primary Analysis; Primary Estimand[1])

Subgroups (n[Tral 300 mg], n[Tral 150 mg], n[P])	Tralokinumab 300 mg Q2W (N=97)	Tralokinumab 150 mg Q2W (N=98)	Placebo (N=94)	Difference from Placebo (95% CI) 300 mg Q2W	Difference from Placebo (95% CI) 150 mg Q2W
Sex					
Male (47, 51, 51)	26%	31%	2%	24% (11%, 37%)	29% (16%, 43%)
Female (50, 47, 43)	30%	26%	12%	28% (2%, 34%)	14% (-2%, 30%)
Race					
White (46, 55, 53)	29%	25%	6%	23% (10%, 36%)	20% (7%, 33%)
Black or African Americans (14, 7, 11)	29%	29%	9%	19% (-10%, 49%)	19% (-18%, 57%)
Asian (20, 28, 23)	25%	32%	4%	21% (<0%, 41%)	28% (9%, 47%)
Other (2, 2, 3)	0%	0%	33%	-33% (-87%, 20%)	-33% (-87%, 20%)
Missing (5, 6, 4)	40%	50%	0%	40% (-3%, 83%)	50% (10%, 90%)
Baseline IGA					
Moderate (49, 54,51)	33%	39%	10%	23% (7%, 38%)	29% (14%, 44%)
Severe (48, 44, 43)	23%	16%	2%	21% (8%, 33%)	14% (2%, 25%)
Overall	**28%**	**29%**	**6%**	**21% (11%, 32%)**	**22% (12%, 32%)**

Source: Statistical Reviewer's Analysis; ADIGA.xpt, ADEASI.xpt

[1] Full Analysis Set (FAS) was defined as all randomized subjects who were dosed with sites 340 and 341 removed. Subjects who received rescue medication considered non-responders; Subjects with missing data at Week 16 imputed as non-responders

Abbreviations: CI; Confidence Interval; IGA, Investigator's Global Assessment; FAS, full analysis set

8.1.9.2. Geographical Location (Country)

ECZTRA 6 was conducted in 10 countries (United States, Canada, Japan, Australia, Great Britain, Netherlands, Germany, Belgium, France, and Poland). Table 18 presents the efficacy results for IGA 0/1 and EASI-75 at Week 16 by country. 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.

Table 18: IGA 0/1 and EASI 75 Response at Week 16 by Country – ECZTRA 6 (FAS; Primary Analysis; Primary Estimand[1])

	IGA 0/1			EASI 75		
	Tralokinumab			Tralokinumab		
Country (n[Tral 300 mg], n[Tral 150 mg], n[P])	**300 mg (N=97)**	**150 mg (N=98)**	**Placebo (N=94)**	**300 mg (N=97)**	**150 mg (N=98)**	**Placebo (N=94)**
United States (28, 31, 35)	21%	23%	6%	32%	35%	9%
Poland (19, 20, 15)	32%	30%	13%	32%	40%	13%
Canada (20, 19, 12)	10%	16%	0%	35%	16%	8%
Japan (11, 10, 11)	0%	40%	0%	9%	50%	0%
Australia (5, 5, 4)	0%	0%	0%	0%	0%	0%
Netherlands (4, 4, 5)	0%	0%	0%	0%	0%	0%
Germany (5, 4, 2)	40%	0%	0%	40%	0%	0%
Belgium (2, 3, 3)	0%	0%	0%	0%	0%	0%
France (2, 2, 4)	50%	50%	0%	50%	50%	0%
Great Britain (1, 0, 3)	0%	0%	0%	100%	0%	0%
Overall	18%	21%	4%	28%	19%	6%

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADAE.xpt
[1] Full Analysis Set (FAS) was defined as all randomized subjects who were dosed with sites 340 and 341 removed. Subjects who received rescue medication considered non-responders; Subjects with missing data at Week 16 imputed as non-responders

8.1.10. Comparison with Results for AD in Adult Subjects

Table 19 presents the results for the IGA 0/1 and EASI-75 endpoints at Week 16 for the two pivotal monotherapy phase 3 trials used to approve tralokinumab for the treatment of moderate to severe AD in adult subjects who are candidates for systemic therapy (Trials ECZTRA 1 and ECZTRA 2), as well as Trial ECZTRA 6 for adolescent subjects. The results are presented for the FAS population using the primary analysis for the primary estimand described in Section 8.1.3. It should be noted that the trials in adults evaluated a single dose of tralokinumab (300 mg Q2W), while the trial in adolescents evaluated two doses of tralokinumab (300 mg Q2W and 150 mg Q2W). Table 19 presents results for the common dose across the trials, i.e., 300 mg Q2W. The treatment effect for the 300 mg dose was similar between adult and adolescent subjects.

Table 19: Results for Efficacy Endpoints at Week 16 in Monotherapy Trials ECZTRA 1, ECZTRA 2 and ECZTRA 6 (FAS; Primary Analysis; Primary Estimand[1])

Trial	Tralokinumab 300 mg Q2W	Placebo	Treatment Effect
ECZTRA 1	N=601	N=197	
IGA 0/1	16%	7%	9%
EASI-75	25%	13%	12%
ECZTRA 2	N=577	N=193	
IGA 0/1	21%	9%	12%
EASI-75	33%	10%	22%
ECZTRA 6	N=97	N=94	
IGA 0/1	18%	6%	14%
EASI-75	28%	6%	22%

Source: Integrated Review for BLA 761180 and Statistical Reviewer's Analysis

[1] Full Analysis Set (FAS) was defined as all randomized subjects who were dosed with sites 340 and 341 removed. Subjects who received rescue medication considered non-responders; Subjects with missing data at Week 16 imputed as non-responders

Abbreviations: EASI-75, at least 75% reduction in Eczema Area and Severity Index score; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety evaluation of ADBRY (tralokinumab 150 mg solution for subcutaneous injection) for the treatment of adolescent subjects with moderate to severe AD relied on safety data from one Phase 3 trial (LP0162-1334, ECZTRA 6). Trial ECZTRA 6 randomized 301 subjects in a 1:1:1 ratio at baseline, of which 289 subjects were included in the safety analysis set for the initial treatment period (weeks 0-16). Supportive safety data for TEAEs in adolescent subjects treated with ADBRY was submitted for 127 subjects who completed ECZTRA 6 and rolled-over to the ongoing long- term safety study ECZTEND, and for 20 adolescent subjects with asthma who received a single dose of tralokinumab in the Phase 1 Study CD-RI-CAT-354-1054.

Additionally, the Applicant provided comparative analyses between the frequency of reported TEAEs for adolescent subjects in Trial ECZTRA 6 and adult subjects in the AD pool/Monotherapy pool (initial treatment periods); and for ECZTRA 6 and the Monotherapy pool (open-label treatment period) in M 2.7.4 (Appendix 1). The Exposure Adjusted Incidence Rates (EAIRs) for safety data referred to in this review were submitted by the Applicant and have not been independently calculated or verified by the clinical or statistical review teams for this efficacy supplement. The EAIRs were used to identify general trends and for comparisons of the reported frequencies of adverse events among different treatment groups in the ECZTRA 6 trial, or between adolescent patients in the ECZTRA 6 trial and adult patients in the AD pool/monotherapy pool submitted under the original BLA.

The safety population included all randomized subjects who used the study drug at least once. In Trial ECZTRA 6, 276 subjects were exposed to tralokinumab at 150 mg Q2W or Q4W; or 300 mg Q2W or Q4W (235.3 patient-years of exposure [PYE]), including 166 subjects exposed for ≥ 52 weeks, and 239 subjects for ≥ 36 weeks.

To determine the safety profile of ADBRY for the treatment of moderate to severe AD in adolescent subjects, the review team analyzed the data for exposure, demographics, baseline characteristics, TEAEs [including severe TEAEs, serious adverse events (SAEs), TEAEs leading to discontinuation (AELD)], physical examinations, clinical laboratory measurements (chemistry, hematology, urinalysis, and serum or urine pregnancy tests for female subjects of child-bearing potential), vital signs (BP, HR, T), electrocardiograms (ECG), psychiatric and suicidality assessment (C-SSRS), Anti-drug Antibodies, and screening laboratory measurements for HIV and Hepatitis B, C.

Adverse Events of Special Interest (AESIs) were prespecified in all ECZTRA Trial protocols (including ECZTRA 6). The following AESIs (based on potential or established safety areas of interest for treatment of AD with monoclonal antibodies) were captured on the AE form:

- 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.
- Eye disorders (conjunctivitis, keratoconjunctivitis, and keratitis).

8.2.2. Review of the Safety Database

Overall Exposure

Overall exposure to ADBRY in Trial ECZTRA 6 in terms of frequency, duration and target population was adequate for the evaluation of safety. Of the 301 subjects randomized, 289 subjects were treated with study drug during initial period, 273 completed Week 16 visit, and 247 subjects completed Week 52 visit (ECZTRA 6 CTR, Figures 2.3, 2.9, 2.10, and 2.14). Refer to Section 8.1 of this review for additional details of Subject Disposition.

The Demographic Characteristics of subjects at baseline were well-balanced across treatment groups in Trial ECZTRA 6 and was representative of the target population.

Adequacy of the safety database:

The safety database presented by the applicant is adequate to characterize the safety profile of ADBRY for the treatment of adolescent subjects with moderate to severe AD. Safety assessments were reasonable and consistent with known adverse events for ADBRY in the target population:

• The size of safety database is adequate.
• The total subject exposure to ADBRY in Trial ECZTRA 6 provides adequate data for the evaluation of safety.
• The demographics of the study population are sufficiently representative of the target population as presented in the following Table:

Table 20: Demographic and Baseline Characteristics (safety analysis set)

	AD Pool (n=2285)	ECZTRA 6 (n=289)
Age (Years)		
Median Age (range)	35.0 (18–92)	15.0 (12–17)
Age group, n (%)		
12-14	0	131 (45.3%)
15-17	0	158 (54.7%)
18-64	2176 (95.2%)	0
≥ 65	109 (4.8%)	0
Sex, n (%)		
Male	1296 (57.7%)	149 (51.6%)
Race, n (%)		

White	1519 (66.5%)	164 (56.7%)
Black or African American	219 (9.6%)	32 (11.1%)
Asian	467 (20.4%)	71 (24.6%)
Native Hawaiian or other Pacific Islander	11 (0.5%)	4 (1.4%)
American Indian or Alaska native	3 (0.1%)	3 (1.0%)
other/multiple	52 (2.3%)	15 (5.2%)
missing	14 (0.6%)	0
Ethnicity, n(%)		
Hispanic or Latino	169 (7.4%)	25 (8.7)
Not Hispanic or Latino	2111 (92.4%)	264 (91.3)
Weight		
Mean body weight (Kg)	77.1	61.5
BSA (%)		
Mean % BSA affected by AD	50.7%	51.1%
Baseline IGA, n (%)		
Moderate (3)	1202 (52.6%)	154 (53.3%)

Source: adapted from sBLA 761180-S001, M 2.7.4 (Summary of Clinical Safety Addendum), Section 1.3, Panel 5; Initial M 2.7.4 Panel 22. Consistent with Clinical Reviewer's JMP Clinical 8.1 analysis. Abbreviations: BSA = body surface area; IGA = Investigator Global Assessment.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of data submitted is adequate to characterize the safety and efficacy of ADBRY subcutaneous injections administered biweekly for the treatment of adolescent subjects with moderate to severe AD. The review team discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

An Adverse Event (AE) was defined as any untoward medical occurrence, including illness, sign, symptoms, clinically significant laboratory abnormalities, or disease temporally associated with the use of the drug, in a subject administered the drug product. AEs did not necessarily have a causal relationship to the study drug. AEs were recorded from the time of first trial-related activity after the informed consent was signed. Treatment Emergent Adverse Events (TEAEs) were AEs that occurred after the first administration of the study drug. TEAEs were followed up until the final outcome of the TEAE is determined during Trial and for up to

2 weeks after the subject completed or discontinued the Trial. TEAEs were documented at each study visit during the Initial and the Maintenance/Open-label periods.

The investigators categorized AEs by system-organ-class (SOC) and preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. The applicant assessed TEAEs by the number of subjects reporting one or more adverse events. Each subject reporting a TEAE was counted once at each level of MedDRA summarization (PT or SOC). Both verbatim terms and preferred terms were included in the data files for Trial ECZTRA 6. There was good correlation between the verbatim and preferred terms used. No new safety signals emerged from the review of TEAEs.

Investigators categorized AEs for seriousness, causality, event name (diagnosis/signs and symptoms), duration, maximum intensity (severity), action taken regarding the study drug (including any treatment given), and outcome of AEs.

Serious Adverse Events (SAEs) were any AE that resulted in death, was immediately life-threatening, required (or prolonged) hospitalization, resulted in persistent disability or incapacity, resulted in a congenital anomaly or birth defect, or a medically important event that may have required medical or surgical intervention to prevent one of the outcomes listed above.

Severity of AEs were assessed by investigators as mild (usually transient, may require only minimal treatment or therapeutic intervention, and does not generally interfere with usual activities of daily living), moderate (usually alleviated with additional specific therapeutic intervention, interferes with usual activities of daily living, and causes discomfort but poses no significant or permanent risk of harm to the subject), or severe (interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention).

Causality of AEs (relationship to study drug assessed by investigators as probably related, possibly related, or unrelated) were based on a reasonable temporal sequence from study drug administration, whether the AE could be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies; and whether the AE followed a known pattern of response to the study drug, disappeared or decreased on cessation or reduction in dose and/or reappeared or worsened upon re-challenge with the study drug.

Adverse Events of Special Interest (AESIs) prespecified in the protocol for Trial ECZTRA 6 included Eczema herpeticum (EH), Malignancies (excluding BCC, localized SCC of the skin, and carcinoma in situ of the cervix), Skin infections requiring systemic treatment, and Eye disorders (conjunctivitis, keratoconjunctivitis, and keratitis).

The Applicant's assessment of AEs conducted for trial ECZTRA 6 appears reasonable and appropriate. The Applicant reported accurate definitions of TEAEs, SAEs, and severity of AEs.

Routine Clinical Tests

The Applicant performed clinical laboratory evaluations (screening serology, chemistry, lipid panel, hematology, urinalysis, and serum/urine pregnancy tests) according to the schedule of trial procedures (ECZTRA 6 CSR, Panels 4-7).

8.2.4. Safety Results

Deaths
No deaths were reported during the ECZTRA 6 clinical trial. A 16 year-old male subject in the long term safety study ECZTEND (# (b) (6)) died following a traffic accident (unrelated to study drug).

Serious Adverse Events

In general, the frequency of reported SAEs in trial ECZTRA 6 were similar to those reported in the AD pool for adult subjects, and no pattern of SOCs/PTs for SAEs were identified. SAEs were reported for 19 subjects during ECZTRA 6 trial, including 5 subjects (5.3%, 17.9/100 PYE) in the placebo group [Infectious mononucleosis (1), Dermatitis Atopic (1), Acute respiratory failure (1), Asthma(1) , Anaphylactic reaction (1) to peanut)], and the following 14 SAEs in the ADBRY-treated groups (listed in the following table):

- Initial treatment period: 4 SAEs (2.1%, 6.8/100 PYE) were reported in the combined ADBRY dosing groups (300 mg Q2W or 150 mg Q 2W): The frequency and EAIRs reported for SAEs were similar to those reported for ADBRY-treated adult subjects in the AD pool (2.1%, 7.4/100 PYE).
- Maintenance period: no SAEs were reported.
- Open-label period: 7 SAEs (3.0%, 4.63/ 100 PYE) were reported for subjects treated with ADBRY 300 mg Q2W + optional TCS; similar to the EAIRs reported for ADBRY-treated adult subjects in the Monotherapy pool (3.8%, 7.4/100 PYE).
- Safety follow-up period: 3 SAEs (1.5%, 6.56/per 100 PYE) were reported in subjects who had been treated with ADBRY in the open-label period.

Additionally, during ECZTEND Study, 1 SAE of hypertension was reported in a subject with history of high blood pressure and recurrent headaches who was hospitalized for COVID-19 infection. This SAE was considered mild, led to temporary drug discontinuation, unlikely related to study drug, and the outcome was reported as recovered/resolved.

The following Table lists the SAEs reported for subjects treated with ADBRY during ECZTRA 6 Trial:

Table 21: Serious Adverse Events (SAE) in subjects treated with ADBRY during ECZTRA 6 Trial:

Subject ID/ Age (years)/ Sex	PT(s)	Severity	Causality	Action taken with study drug	Outcome
Initial period					
(b) (6) 16, F	Cerebrovascular accident	Severe	Not Related	Drug Withdrawn	Recovered/ Resolved With Sequelae
(b) (6) 16, F	Cellulitis	Severe	Not Related	Dose Not Changed	Recovered/ Resolved
(b) (6) 16, F	Dermatitis atopic	Severe	Not Related	Dose Not Changed	Recovered/ Resolved
(b) (6) 13, M	Radius fracture	Moderate	Not Related	Dose Not Changed	Recovered/ Resolved
Open-label period					
(b) (6) 16, M	Obsessive-compulsive disorder	Moderate	Not Related	Dose Not Changed	Recovered/ Resolved
(b) (6) 17, M	Anaphylactic reaction (tree nut)	Severe	Not Related	Dose Not Changed	Recovered/ Resolved
(b) (6) 12, M	Appendicitis perforated	Severe	Not Related	Dose Not Changed	Recovered/ Resolved
(b) (6) 13, F	Anorexia nervosa	Severe	Not Related	Dose Not Changed	Recovering/ Resolving
(b) (6) 13, F	Suicidal ideation	Moderate	Not Related	Dose Not Changed	Recovered/ Resolved With Sequelae
(b) (6) 15, M	Concussion	Moderate	Not Related	Dose Not Changed	Recovered/ Resolved
(b) (6) 17, F	Gastritis	Moderate	Possibly Related	Dose Not Changed	Recovered/ Resolved
Safety follow-up period					
(b) (6) 13, F	Intentional overdose	Severe	Not Related	Not Applicable	Recovered/ Resolved
(b) (6) 13, F	Renal injury	Severe	Not Related	Not Applicable	Recovered/ Resolved
(b) (6) 16, M	Anaphylactic reaction (Food)	Severe	Not Related	Not Applicable	Recovered/ Resolved

Source: Adapted from CTR LP0162-1334 (ECZTRA 6), Appendix 2.7, listing 7.3. MedDRA 20.0. Consistent with Clinical Reviewer's JMP Clinical 8.1 analysis.

An SAE of "Cerebrovascular accident" in a 16-year-old female subject (Subject ID: (b) (6)) was reported on Day 58 and led to hospitalization and discontinuation from treatment. Subject's history included Kawasaki disease, proximal LAD coronary dilation, (+) lipoprotein A, hyperlipidemia, prediabetes, and (+) MOG antibody. This SAE was considered not related to the study drug.

Dropouts and/or Discontinuations Due to Adverse Effects

During the initial treatment period of ECZTRA 6 Trial, one AE leading to drug discontinuation (AELD) of "cerebrovascular accident" was reported in the combined ADBRY-treated group at an EAIR of 1.7/ 100 PYE, compared to the AELD EAIR of (9.0/ 100 PYE) for the ADBRY-treated group in the initial period for AD pool in adult patients. This AELD was also reported as an SAE (Subject ID: (b) (6)).

No AELDs were reported during the maintenance treatment period.

During the open-label treatment period of ECZTRA 6 Trial, 2 AELDs of "foreign body sensation in eyes" (1), and "procedural anxiety" (1) were reported at an EAIR of 1.3/ 100 PYE, compared to the EAIR of 4.5/ 100 PYE for the open-label period for monotherapy pool in adult patients. Both AELDs were non-serious, moderate in severity, and possibly or probably related to ADBRY.

During ECZTEND study, one additional AELD of "Dermatitis atopic" was reported as a non-serious, mild in severity, related to ADBRY, with the outcome of recovering/resolving.

Significant Adverse Events

Severe AEs

During the initial treatment period of ECZTRA 6 trial, severe AEs were reported for the combined ADBRY-treated groups at an EAIR of 23.8/ 100 PYE, compared to EAIR of 20.2/ 100 PYE for the ADBRY-treated group in the initial period for AD pool.

During the open-label period, severe AEs were reported at an EAIR of 2.6/ 100 PYE, compared to the EAIR of 11.3/ 100 PYE for the open-label period for monotherapy pool in adult patients.

Adverse Events of Special Interest (AESIs)

During the initial treatment period, the frequency of AESIs (per 100 patient-years of Exposure [/100 PYE]) reported for the combined ADBRY dosing groups in ECZTRA 6 trial for adolescent subjects were similar to (for EH and Malignancies (excluding BCC, localized SCC and CIS of

cervix)), or lower (for Eye disorders) than their respective frequencies reported for adult subjects in the AD pool. The EAIR for skin infections requiring systemic treatment was higher for adolescent subjects; however, for the 300 mg Q2W dose group in the ECZTRA 6 trial, the EAIR (10.2/ 100 PYE) was similar to the EAIR for adult subjects in the AD pool (9.7/ 100 PYE).

During the open-label treatment period, the frequency of AESIs reported for the ADBRY 300 mg Q2W+TCS group in the ECZTRA 6 Trial was lower than their respective frequencies reported for adult subjects in the monotherapy pool.

The EAIRs (/100 PYE) for AESIs in the ECZTRA 6 and their corresponding safety pools in adult subjects are summarized in the following Table:

Table 22: Summary of AESI EAIRs (/100 PYE) - initial treatment period - AD pool vs ECZTRA 6 - adjusted pooling – safety analysis set

Treatment Period	Initial period (Weeks 0-16)				Open-label period (weeks 16-52)	
Trial or Safety pool	ECZTRA 6		AD pool		ECZTRA 6	Monotherapy pool
Dose group	Adbry (150 mg or 300 mg Q2W) (n=195, PYE=58.81)	Placebo Q2W (n=94, PYE=27.93)	Adbry (300 mg Q2W) (n=1605, PYE=473.21)	Placebo Q2W (n=680, PYE=193.1)	Adbry (300 mg Q2W) + optional TCS(n=234, PYE=151.12)	Adbry (300 mg Q2W) + optional TCS (n=1121, PYE=664.92)
AESI Category						
Eczema herpeticum	1.7	3.6	1.2	5.2	0	1.4
Malignancies (excluding BCC, localized SCC of the skin, and carcinoma in situ of the cervix)	0	0	0.2	0	0	0.3
Skin infections requiring systemic treatment	17.0	7.2	9.7	22.8	6.0	7.1
Eye disorders (conjunctivitis, keratoconjunctivitis, and keratitis)	13.6	10.7	31.1	12.9	9.9	17.9

Source: BLA 761180-S001 (SDN 64), M 2.7.4 SCS-Addendum, Panels 12-13, Appendix Table 2.2.6.

Other Adverse Events of Interest (AEOI)

AEOIs were based on pre-defined MedDRA search criteria for the ECZTRA 6 and AD trials in adult subjects.

In general, the EAIRs for AEOIs were similar between adolescent subjects in the ECZTRA 6 trial and adult subjects in the AD pool (for the initial treatment period) and the monotherapy pool (for the open-label period), as summarized in the following Table:

Table 23 Summary of other AEs of interest EAIRs (/100 PYE) - initial treatment period - AD pool vs ECZTRA 6 - adjusted pooling – safety analysis set

Treatment Period	Initial period (Weeks 0-16)				Open-label period (weeks 16-52)	
Trial or Safety pool	ECZTRA 6		AD pool		ECZTRA 6	Monotherapy pool
Dose group	Adbry (150 mg or 300 mg Q2W) (n=195, PYE=58.81)	Placebo Q2W (n=94, PYE=27.93)	Adbry (300 mg Q2W) (n=1605, PYE=473.21)	Placebo Q2W (n=680, PYE=193.1)	Adbry (300 mg Q2W)+ optional TCS (n=234, PYE=151.12)	Adbry 300 mg Q2W) + optional TCS (n=1121, PYE=664.92)
AEOI Category						
Anaphylaxis	0	0	0	0	0	0
Serious allergic reactions	1.7	7.2	1.5	2.1	0.7	0.8
Immune complex disease	0	0	0	0.6	0	0
Injection site reactions	49.3	3.6	51.5	21.3	26.5	37.0
Serious infections	1.7	3.6	1.3	3.7	0.7	1.2
Severe infections	3.4	0	2.1	5.8	0.7	1.4
Medication errors	3.4	0	4.0	2.5	1.3	1.4
Suicidality and psychiatric disorders	1.7	0	0.4	0	2.6	0
Rare adverse events	0	3.6	2.2	1.3	0.7	1.1
Cardiovascular events of interest	1.7	0	0	0	0	0.5
Malignancy	0	0	2.6	2.6	0	1.1

Source: BLA 761180-S001 (SDN 64), M 2.7.4 SCS-Addendum, Panel 14, Appendix Table 2.2.6.

Treatment Emergent Adverse Events and Adverse Reactions

Initial Treatment Period

In general, the frequency of TEAEs reported during the initial period of ECZTRA 6 were similar to the initial period of AD pool in adult patients. Most AEs were not serious, not severe, not related to the study drug, and not AELDs; resulted in no action by the investigators and were reported as recovered/resolved as summarized in the following Table.

Table 24 Overall summary of AEs - initial treatment period - AD pool vs ECZTRA 6 - adjusted pooling - safety analysis set

Trial or Safety pool	ECZTRA 6		AD pool
Dose group	Adbry (150 mg or 300 mg Q2W) dose groups combined (n=195, PYE=58.81)	Placebo Q2W (n=94, PYE=27.93)	Adbry (300 mg Q2W) (n=1605, PYE=473.21)
AE category	N, (%), EAIR/100 PYE	N, (%), EAIR/100 PYE	N, (%), adj. EAIR/100 PYE
TEAE	129, (66.2%), 518.6	58, (61.7%), 479.7	1082, (65.9%), 640.7
SAE	4, (2.1%), 6.8	5, (5.3%), 17.9	37, (2.1%), 7.4
Severe AE	8, (4.1%), 23.8	7, (7.4%), 25.1	77, (4.6%), 20.2
Related to study drug*	51, (26.2%), 158.1	20, (21.3%), 128.9	464, (28.0%), 207.9
AELD	1, (0.5%), 1.7	0	35, (2.1%), 9.0

Source: Adapted from M 2.7.4 Addendum (SCS)- Panel 6.
*Related to study drug comprise AEs considered possibly related or probably related by the investigator.

The most frequently reported TEAEs during the initial periods of ECZTRA 6 and AD pools are summarized in the following Table:

Table 25 Summary of TEAEs reported in **(≥3%)** of subjects treated with ADBRY (combined dose groups) compared to vehicle group in ECZTRA 6, and AD pool by SOC and PT- initial treatment period (adjusted pooling – safety analysis set)

Trial or Safety pool	ECZTRA 6		AD pool
Dose group	Adbry (150 mg or 300 mg Q2W) dose groups combined (n=195, PYE=58.81)	Placebo Q2W (n=94, PYE=27.93)	Adbry (300 mg Q2W) (n=1605, PYE=473.21)
SOC/PT	N, (%), EAIR/100 PYE	N, (%), EAIR/100 PYE	N, (%), adj. EAIR/100 PYE
Infections and infestations			
Viral upper respiratory tract infection	31, (15.9%), 64.6	8 (8.5%) 35.8	256, (15.7%), 65.1
upper respiratory tract infection	19, (9.7%), 35.7	4 (4.3%) 17.9	92 (5.6%) 20.8
Conjunctivitis	2, (1.0%), 3.4	0	90 (5.4%) 21.0
Skin and subcutaneous tissue disorders			
Dermatitis atopic	20, (10.3%), 40.8	12 (12.8%) 57.3	272 (15.4%) 68.0
General disorders and administration site conditions			
Injection site reaction	8, (4.1%), 20.4	0	58 (3.5%) 22.9
Injection site pain	7, (3.6%), 22.1	1 (1.1%) 3.6	39 (2.3%) 13.4
Nervous system disorders			
Headache	11, (5.6%), 18.7	3 (3.2%) 10.7	72 (4.6%) 21.6

Source: Adapted from M 2.7.4 Addendum (SCS)- Panel 7, Appendices Tables 2.1.3, 2.1.4, 2.1.9, 2.1.10

Maintenance Period

Of the 273 subjects who completed the initial treatment period in ECZTRA 6, 56 subjects were responders at Week 16 and were re-randomized (1:1 as Q2W or Q4W) to receive the same ADBRY dose that they had received Q2W in the initial period (between 11-14 subjects in each group), or placebo Q2W (6 subjects). An additional 20 subjects were transferred from the maintenance to the open-label treatment after Week 16. In general, the frequency and distribution of AEs by SOC/PT reported during maintenance periods for ECZTRA 6 and the monotherapy pool in adult subjects were similar.

Open-label Period

Of the 273 subjects who completed the initial treatment period in ECZTRA 6, 214 subjects

were non-responders and were transferred to open-label treatment at W 16. Similar to the initial period, most AEs were not serious, not severe, not related to the study drug, not AELDs, and resulted in no action by the investigators.

In general, the frequency of AEs reported during the open-label period of ECZTRA 6 Trial were lower than those reported during the initial period of ECZTRA 6 and were similar to those for the AEs in the monotherapy pool for adult subjects. The distribution pattern of AEs by SOC/PT were similar between the open-label period of ECZTRA 6 and the monotherapy pool in adult subjects (with a lower frequency reported for AEs of "Dermatitis atopic" and "Conjunctivitis" in ECZTRA 6) as summarized in the following Tables.

Table 26 Overall summary of AEs - open-label treatment period – monotherapy pool vs ECZTRA 6 - simple pooling - open-label safety analysis set

Trial or Safety pool	ECZTRA 6	Monotherapy pool
Dose group	Adbry (300 mg Q2W) + optional TCS (n=234, PYE=151.12)	Adbry (300 mg Q2W) + optional TCS (n=1121, PYE=664.92)
AE category	N, (%), EAIR/100 PYE	N, (%), EAIR/100 PYE
TEAE	158, (67.5%), 349.4	814, (72.6%), 431.6
SAE	7, (3.0%), 4.6	43, (3.8%), 7.4
Severe AE	4, (1.7%), 2.6	47, (4.2%), 11.3
Related to study drug*	65, (27.8%), 107.2	349, (31.1%), 134.9
AELD	2, (0.9%), 1.3	27, (2.4%), 4.5

Source: Adapted from M 2.7.4 Addendum (SCS)- Panel 9

Table 27 Summary of TEAEs reported in **(≥3%** in any treatment group) by SOC/PT - open-label treatment period - monotherapy pool vs ECZTRA 6 - simple pooling - open-label safety analysis set

Trial or Safety pool	ECZTRA 6	Monotherapy pool
Dose group	Adbry (300 mg Q2W) + optional TCS (n=234, PYE=151.12)	Adbry (300 mg Q2W) + optional TCS (n=1121, PYE=664.92)
SOC/PT	N, (%), EAIR/100 PYE	N, (%), adj. EAIR/100 PYE
Infections and infestations		
Viral upper respiratory tract infection	44, (18.8%), 39.7	201, (17.9%), 42.7
upper respiratory tract infection	25, (10.7%), 22.5	78, (7.0%), 15.2
Conjunctivitis	4, (1.7%), 4.0	63, (5.6%), 11.3
Skin and subcutaneous tissue disorders		
Dermatitis atopic	19, (8.1%), 17.2	238, (21.2%), 56.8
Pruritus	2, (0.9%), 1.3	34, (3.0%), 6.5
General disorders and administration site conditions		
Injection site reaction	10, (4.3%), 10.6	40, (3.6%), 15.0
Nervous system disorders		
Headache	12, (5.1%), 11.2	36, (3.2%), 6.9
Respiratory, thoracic and mediastinal disorders		
Cough	9, (3.8%), 6.6	22, (2.0%), 3.5

Source: Adapted from M 2.7.4 Addendum (SCS)- Panels 10, 11

Safety follow-up Period

The frequency of AEs reported during the safety follow-up period of ECZTRA 6 were similar to those reported during the safety follow-up period in the AD pool, and lower than those in the initial or maintenance periods of ECZTRA 6. No AE pattern by SOC/PT was identified.

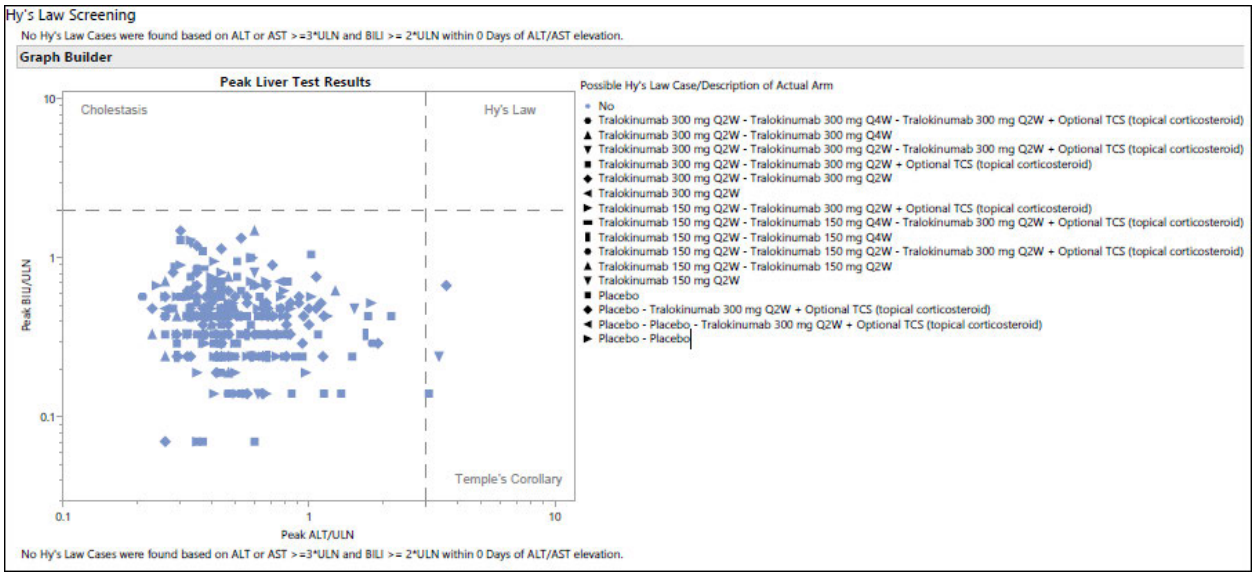
Laboratory Findings

Clinical Chemistry laboratory measurements (electrolytes, renal function, lipid panel, glucose, LDH, IgE) of the mean and mean changes from baseline remained within normal range with minor fluctuations. No clinically significant differences in mean values, potentially clinically significant (PCS) values, and AEs were reported between treatment groups during ECZTRA 6 Trial, consistent with results reported in adult subjects.

Liver parameters measurements during trial ECZTRA 6 did not identify any subjects with potential drug-induced liver injury (DILI) (concurrent elevations of ALT or AST ≥3× ULN and bilirubin ≥2× ULN) or Hy's law. Most PCS values (ALT between 3x to 5x ULN in 2 subjects), (AST between 10X to 20X ULN in 1 subject), (ALP >1.5x ULN in 9 subjects) were not considered clinically significant or reported as AEs. The number of subjects with AEs reported for abnormal liver parameters included: initial period (3), maintenance period (0), open-label period (1), and follow-up period (1). AEs reported for subjects with PCS values of liver parameters were mild in severity, not SAEs or AELDs, and resolved or resolving (1) at the end of Trial. No PCS values of abnormal liver parameters were reported for subjects in the vehicle group.

Hy's Law Screening Report Results

Figure 9- Hy's law screening plot for trial ECZTRA 6

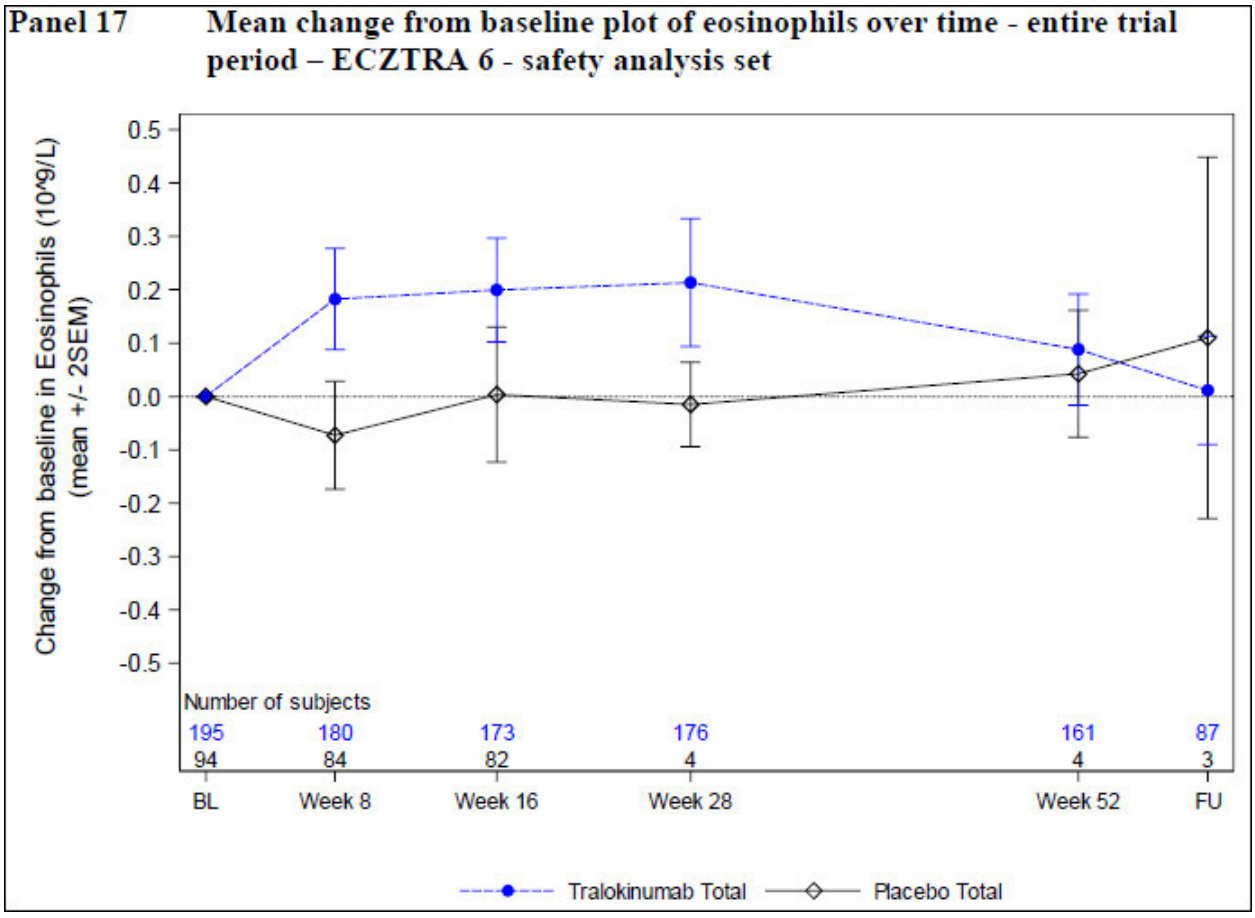


Source: Clinical Reviewer's JMP 14.3.0 and JMP Clinical 8.1 analyses. Report Options Filtering:
Subjects: Select the analysis population: All Subjects Excluding Screen Failures
Domain: Only include on-trial measurements: Yes; Include the following findings records: All

Hematology parameters (other than Eosinophils) measurements of the mean and mean changes from baseline remained within normal range with minor fluctuations. No clinically significant changes in mean values, PCS values, or AEs were reported between treatment groups during ECZTRA 6 Trial, consistent with results reported in adult subjects.

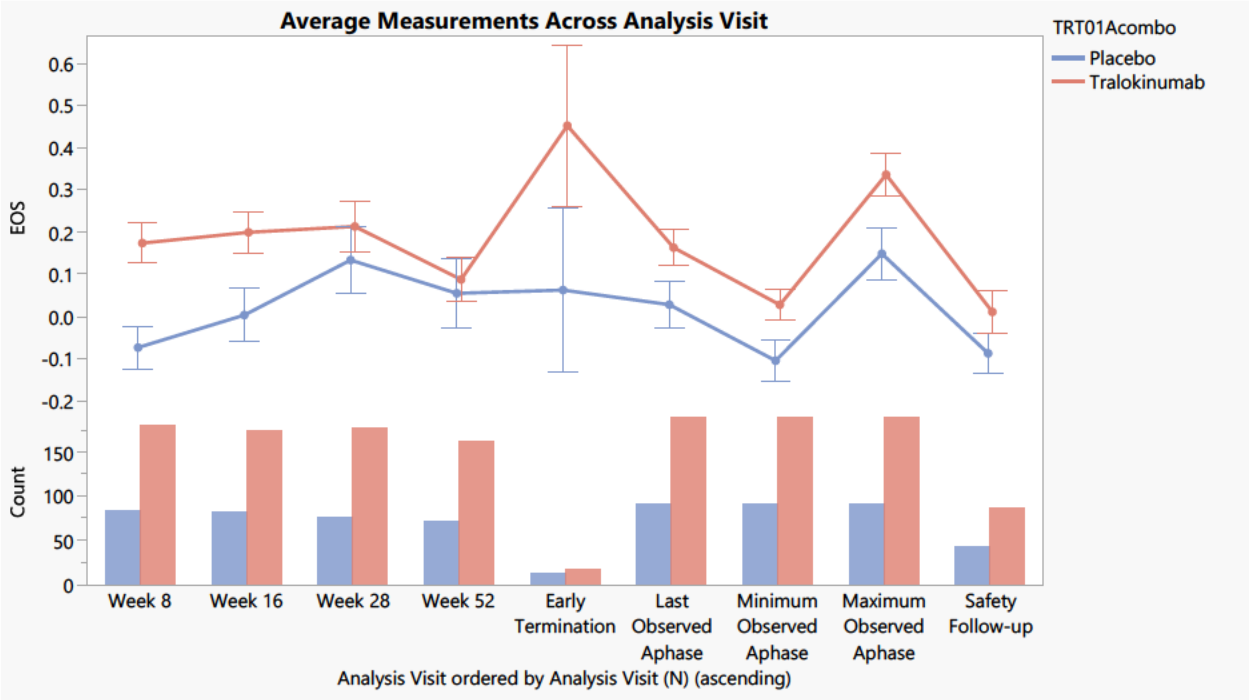
Eosinophil measurements were elevated above ULN (500/ microliter) at baseline for > 40% of subjects, and showed a transient increase in mean (approximately 200/ microliter) with return to baseline value at the end of ECZTRA 6 Trial, consistent with similar results reported in AD pool for adult subjects, as depicted in the following figure:

Figure 10- Mean change from baseline plot of eosinophils over time - entire trial period – ECZTRA 6 - safety analysis set



Source: M 2.7.4 Addendum, Panel 17.

Figure 11- Change from Baseline for Eosinophils (10^9 /L) for the combined tralokinumab dose groups compared to the placebo group over time for duration of trial ECZTRA 6- Safety analysis set



Source: Clinical Reviewer's JMP 14.3.0 and JMP Clinical 8.1 analyses. Tralokinumab 150 mg Q2W and 300 mg Q2W Arms combined vs. Placebo. Report Options Filtering:
Subjects: Select the analysis population: Safety
Domain: Findings Domain Tests for Analysis: EOS
Remove unscheduled visits: No
Include the following findings records: All

PCS values for eosinophils (between 1500 to 5000/microliter) and (> 5000/microliter) were reported at a similar or lower frequency in ECZTRA 6 Trial compared to the AD pool or monotherapy pools in adult subjects. No AE of "eosinophilia" or "eosinophil count increased" were reported in ECZTRA 6; and subjects with elevated eosinophil counts did not show a pattern or clustering of AEs.

Vital Signs

No clinically significant changes in the physical examination or vital signs (DBP, SBP, HR, T) were reported for any treatment group during ECZTRA 6 Trial. AEs related to vital signs included "blood pressure increased" in the initial period (2) and in the open-label period (1)

[not serious or severe]. One subject was reported with 2 non-serious, moderate AEs of "heart rate increased".

Electrocardiograms (ECGs)

No clinically significant changes in ECG parameters were reported during ECZTRA 6 trial.
3 subjects reported with 4 non-serious, non-severe, non-AELD AEs related to ECG in the open-label period, including 1 subject with 2 AEs of "heart rate increased ", AE of "Tachycardia" (1), and an AE of "electrocardiogram QT prolonged" (1).

QT

One AE of "electrocardiogram QT prolonged" was reported in a 16-year-old female subject (ID: (b) (6)) during the open-label period (same subject reported above under ECG). This AE was reported as moderate, possibly related, dose not changed, outcome of recovered/resolved.

8.2.5. Analysis of Submission-Specific Safety Issues

Comparison of AE profiles between tralokinumab 300 mg Q2W vs. 150 mg Q2W dose groups:

At the baseline visit of trial ECZTRA 6, subjects were randomized (1:1:1) to one of 3 treatment groups: placebo Q2W, tralokinumab 150 mg Q2W, and tralokinumab 300 mg Q2W. The following tables provide a comparison of the most frequently reported TEAEs among treatment groups during the initial treatment period:

Table 28- Summary of SAEs by dose group- initial period- safety population

Preferred Term	Placebo (N=94) n (%)	Tralokinumab 150 Q2W (N=98) n (%)	Tralokinumab 300 Q2W (N=97) n (%)
Cellulitis	0 (0.0)	1 (1.0)	0 (0.0)
Cerebrovascular accident	0 (0.0)	1 (1.0)	0 (0.0)
Dermatitis atopic	1 (1.1)	1 (1.0)	0 (0.0)
Acute respiratory failure	1 (1.1)	0 (0.0)	0 (0.0)
Anaphylactic reaction	1 (1.1)	0 (0.0)	0 (0.0)
Asthma	1 (1.1)	0 (0.0)	0 (0.0)
Infectious mononucleosis	1 (1.1)	0 (0.0)	0 (0.0)
Radius fracture	0 (0.0)	0 (0.0)	1 (1.0)

Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Tralokinumab 150 Q2W" and SAFFL = "Y" (Tralokinumab 150 Q2W); TRT01A = "Tralokinumab 300 Q2W" and SAFFL = "Y" (Tralokinumab 300 Q2W); TRTEMFL = "Y" and APHASE = "INITIAL" and AESER = "Y" (Adverse Events).

Table 29- Summary of TEAEs **(≥1%)** by Maximum Severity-Toxicity by dose group- initial period- safety population

Preferred Term	Placebo (N=94)			Tralokinumab 150 Q2W (N=98)			Tralokinumab 300 Q2W (N=97)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Dermatitis atopic	1 (1.1)	8 (8.5)	3 (3.2)	2 (2.0)	8 (8.2)	3 (3.1)	1 (1.0)	5 (5.2)	1 (1.0)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	3 (3.2)	1 (1.1)	0 (0.0)	2 (2.0)	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)
Vomiting	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)

Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer. Adverse events missing severity/toxicity grades are not included in the above table.
Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Tralokinumab 150 Q2W" and SAFFL = "Y" (Tralokinumab 150 Q2W); TRT01A = "Tralokinumab 300 Q2W" and SAFFL = "Y" (Tralokinumab 300 Q2W); TRTEMFL = "Y" and APHASE = "INITIAL" and AESEV = ("Mild", "Moderate", or "Severe") (Adverse Events).
Percent Threshold: Tralokinumab 150 Q2W - Severe ≥ 1%.

Table 30- Summary of TEAEs Leading to Discontinuation by dose group- initial period- safety population

Preferred Term	Placebo (N=94) n (%)	Tralokinumab 150 Q2W (N=98) n (%)	Tralokinumab 300 Q2W (N=97) n (%)
Cerebrovascular accident	0 (0.0)	1 (1.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Tralokinumab 150 Q2W" and SAFFL = "Y" (Tralokinumab 150 Q2W); TRT01A = "Tralokinumab 300 Q2W" and SAFFL = "Y" (Tralokinumab 300 Q2W); TRTEMFL = "Y" and APHASE = "INITIAL" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

Table 31- Summary of TEAEs - Grouped Terms by dose group- initial period- safety population

Grouped Term	Placebo (N=94) n (%)	Tralokinumab 150 Q2W (N=98) n (%)	Tralokinumab 300 Q2W (N=97) n (%)
Conjunctivitis cluster*	2 (2.1)	4 (4.1)	3 (3.1)
Injection site reactions cluster*	1 (1.1)	9 (9.2)	7 (7.2)
Upper respiratory tract infections cluster*	17 (18.1)	27 (27.6)	22 (22.7)

Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Tralokinumab 150 Q2W" and SAFFL = "Y" (Tralokinumab 150 Q2W); TRT01A = "Tralokinumab 300 Q2W" and SAFFL = "Y" (Tralokinumab 300 Q2W); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).
Conjunctivitis cluster* includes: Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial.
Injection site reactions cluster* includes: Injection site oedema, Injection site pain, Injection site reaction, Injection site swelling, Injection site urticaria.
Upper respiratory tract infections cluster* includes: Nasopharyngitis, Pharyngitis, Upper respiratory tract infection, Viral upper respiratory tract infection.

Table 32- Summary of TEAEs **(≥2%)** by Preferred Term (PT) and by dose group- initial period-safety population

Preferred Term	Placebo (N=94) n (%)	Tralokinumab 150 Q2W (N=98) n (%)	Tralokinumab 300 Q2W (N=97) n (%)
Viral upper respiratory tract infection	8 (8.5)	19 (19.4)	12 (12.4)
Dermatitis atopic	12 (12.8)	13 (13.3)	7 (7.2)
Upper respiratory tract infection	4 (4.3)	8 (8.2)	11 (11.3)
Injection site reaction	0 (0.0)	6 (6.1)	2 (2.1)
Headache	3 (3.2)	5 (5.1)	6 (6.2)
Fatigue	4 (4.3)	4 (4.1)	0 (0.0)
Dyspepsia	0 (0.0)	3 (3.1)	0 (0.0)
Injection site pain	1 (1.1)	3 (3.1)	4 (4.1)
Insomnia	1 (1.1)	3 (3.1)	1 (1.0)
Nausea	0 (0.0)	3 (3.1)	1 (1.0)
Bronchitis	0 (0.0)	2 (2.0)	2 (2.1)
Conjunctivitis	0 (0.0)	2 (2.0)	0 (0.0)
Conjunctivitis allergic	2 (2.1)	2 (2.0)	2 (2.1)
Cystitis	0 (0.0)	2 (2.0)	1 (1.0)
Diarrhoea	3 (3.2)	2 (2.0)	1 (1.0)
Ear infection	2 (2.1)	2 (2.0)	0 (0.0)
Influenza	1 (1.1)	2 (2.0)	2 (2.1)
Pharyngitis	4 (4.3)	2 (2.0)	0 (0.0)
Pyrexia	1 (1.1)	2 (2.0)	0 (0.0)
Sinus congestion	1 (1.1)	2 (2.0)	0 (0.0)
Skin infection	0 (0.0)	2 (2.0)	1 (1.0)
Urticaria	1 (1.1)	2 (2.0)	1 (1.0)
Vomiting	1 (1.1)	2 (2.0)	1 (1.0)

Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRT01A = "Tralokinumab 150 Q2W" and SAFFL = "Y" (Tralokinumab 150 Q2W); TRT01A = "Tralokinumab 300 Q2W" and SAFFL = "Y" (Tralokinumab 300 Q2W); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).
Percent Threshold: Tralokinumab 150 Q2W ≥ 2%.

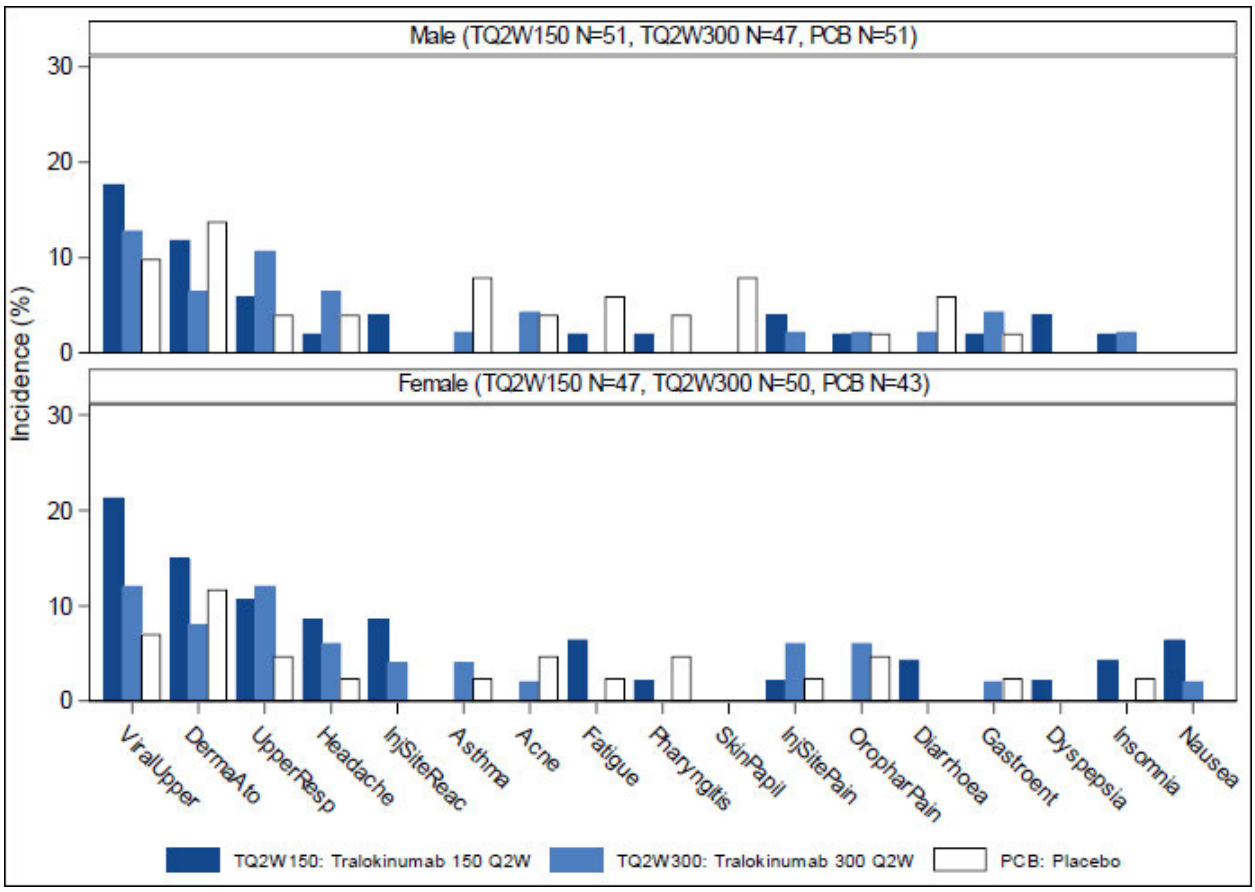
Reviewer's comment
In general, the frequency and distribution of Adverse Events were similar between the tralokinumab 300 mg Q2W and 150 mg Q2W dose groups during the initial period, and no clinically significant differences in the AE profile of the 2 dose groups were identified.

8.2.6. Safety Analyses by Demographic Subgroups

Safety assessments by subgroups (sex, race, age, body weight, baseline IGA, and region) during the initial period of ECZTRA 6 trial did not identify any clinically significant differences between subgroups based of the frequency and SOC/PT distribution of AEs (consistent with similar conclusion for the monotherapy pool in adult subjects), as depicted in the following Bar-plot figures and Tables:

TEAEs by sex

Figure 12- Bar plot of frequent AEs by PT (17 most frequent PTs in any treatment group in the overall population), by sex - initial treatment period - ECZTRA 6 - safety analysis set



Source: M. 2.7.4 Addendum – Appendix 1, Figure 2.4.5:

Table 33- Summary of Grouped PTs for TEAEs in ≥ 2 (4%) subjects in any subgroup by dose and by sex- initial period of ECZTRA 6 trial:

Grouped Term	Placebo-male (N=51) n (%)	Tralokinumab 150 Q2W-male (N=51) n (%)	Tralokinumab 300 Q2W-male (N=47) n (%)	Placebo-female (N=43) n (%)	Tralokinumab 150 Q2W-female (N=47) n (%)	Tralokinumab 300 Q2W-female (N=50) n (%)
Upper respiratory tract infections cluster*	9 (17.6)	12 (23.5)	11 (23.4)	8 (18.6)	15 (31.9)	11 (22.0)
Injection site reactions cluster*	0 (0.0)	4 (7.8)	2 (4.3)	1 (2.3)	5 (10.6)	5 (10.0)
Conjunctivitis cluster*	1 (2.0)	1 (2.0)	2 (4.3)	1 (2.3)	3 (6.4)	1 (2.0)

Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and SEXVAL = "Male" and SAFFL = "Y" (Placebo-male); TRT01A = "Tralokinumab 150 Q2W" and SEXVAL = "Male" and SAFFL = "Y" (Tralokinumab 150 Q2W-male); TRT01A = "Tralokinumab 300 Q2W" and SEXVAL = "Male" and SAFFL = "Y" (Tralokinumab 300 Q2W-male); TRT01A = "Placebo" and SEXVAL = "Female" and SAFFL = "Y" (Placebo-female); TRT01A = "Tralokinumab 150 Q2W" and SEXVAL = "Female" and SAFFL = "Y" (Tralokinumab 150 Q2W-female); TRT01A = "Tralokinumab 300 Q2W" and SEXVAL = "Female" and SAFFL = "Y" (Tralokinumab 300 Q2W-female); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).

Conjunctivitis cluster* includes: Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial.

Injection site reactions cluster* includes: Injection site oedema, Injection site pain, Injection site reaction, Injection site swelling, Injection site urticaria.
Upper respiratory tract infections cluster* includes: Nasopharyngitis, Pharyngitis, Upper respiratory tract infection, Viral upper respiratory tract infection.

Table 34- Summary of TEAEs by PT in ≥ 2 (4%) subjects in any subgroup by dose and by sex- initial period of ECZTRA 6 trial:

Preferred Term	Placebo-male (N=51) n (%)	Tralokinumab 150 Q2W-male (N=51) n (%)	Tralokinumab 300 Q2W-male (N=47) n (%)	Placebo-female (N=43) n (%)	Tralokinumab 150 Q2W-female (N=47) n (%)	Tralokinumab 300 Q2W-female (N=50) n (%)
Upper respiratory tract infection	2 (3.9)	3 (5.9)	5 (10.6)	2 (4.7)	5 (10.6)	6 (12.0)
Viral upper respiratory tract infection	5 (9.8)	9 (17.6)	6 (12.8)	3 (7.0)	10 (21.3)	6 (12.0)
Dermatitis atopic	7 (13.7)	6 (11.8)	3 (6.4)	5 (11.6)	7 (14.9)	4 (8.0)
Headache	2 (3.9)	1 (2.0)	3 (6.4)	1 (2.3)	4 (8.5)	3 (6.0)
Injection site pain	0 (0.0)	2 (3.9)	1 (2.1)	1 (2.3)	1 (2.1)	3 (6.0)
Oropharyngeal pain	1 (2.0)	1 (2.0)	1 (2.1)	2 (4.7)	0 (0.0)	3 (6.0)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)
Asthma	4 (7.8)	0 (0.0)	1 (2.1)	1 (2.3)	0 (0.0)	2 (4.0)
Bronchitis	0 (0.0)	2 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)
Injection site reaction	0 (0.0)	2 (3.9)	0 (0.0)	0 (0.0)	4 (8.5)	2 (4.0)

Table 34- Summary of TEAEs by PT in ≥ 2 (4%) subjects in any subgroup by dose and by sex- initial period of ECZTRA 6 trial:

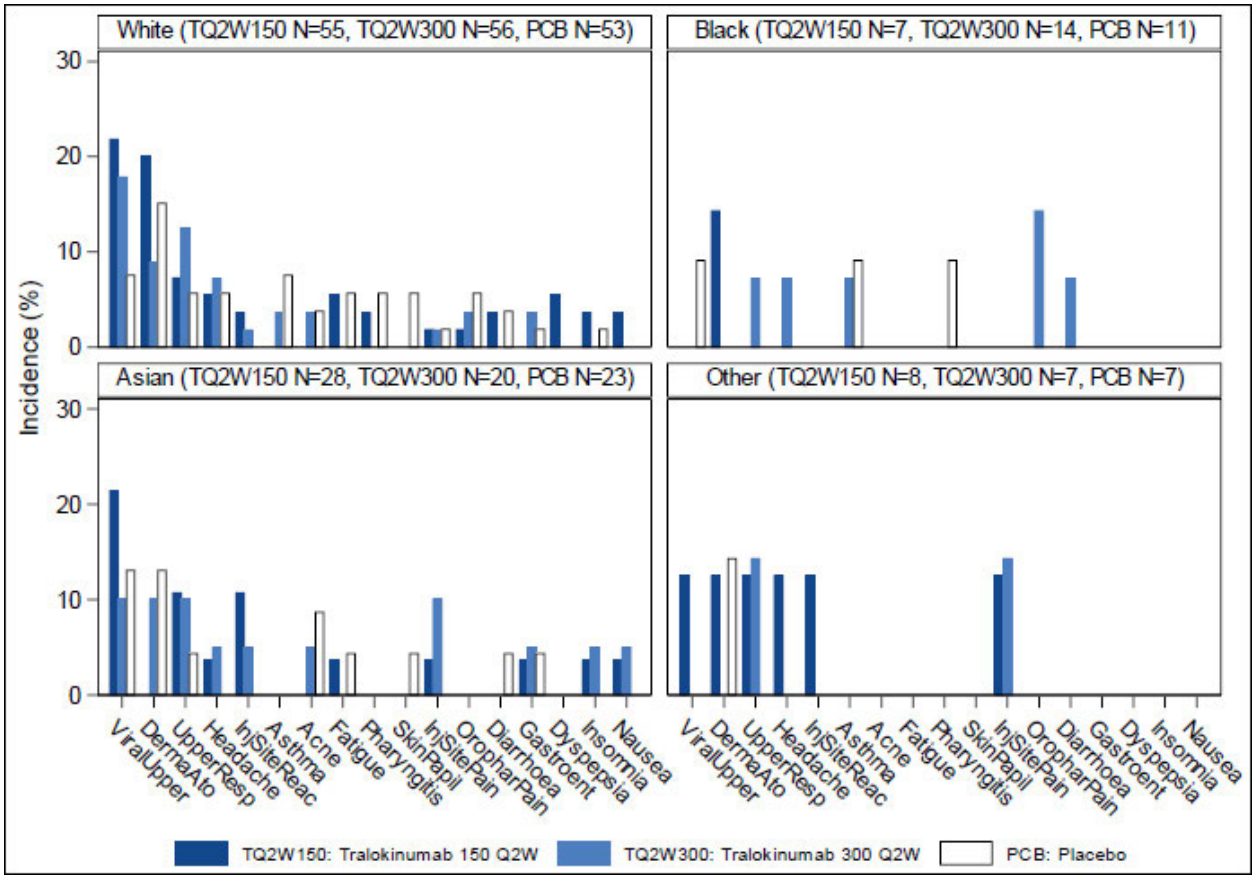
Preferred Term	Placebo-male (N=51) n (%)	Tralokinumab 150 Q2W-male (N=51) n (%)	Tralokinumab 300 Q2W-male (N=47) n (%)	Placebo-female (N=43) n (%)	Tralokinumab 150 Q2W-female (N=47) n (%)	Tralokinumab 300 Q2W-female (N=50) n (%)
Tonsillitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	2 (4.0)
Acne	2 (3.9)	0 (0.0)	2 (4.3)	2 (4.7)	0 (0.0)	1 (2.0)
Gastroenteritis	1 (2.0)	1 (2.0)	2 (4.3)	1 (2.3)	0 (0.0)	1 (2.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.4)	1 (2.0)
Vomiting	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.3)	1 (2.0)
Conjunctivitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.3)	0 (0.0)
Conjunctivitis allergic	1 (2.0)	1 (2.0)	2 (4.3)	1 (2.3)	1 (2.1)	0 (0.0)
Cystitis	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	2 (4.3)	0 (0.0)
Diarrhoea	3 (5.9)	0 (0.0)	1 (2.1)	0 (0.0)	2 (4.3)	0 (0.0)
Fatigue	3 (5.9)	1 (2.0)	0 (0.0)	1 (2.3)	3 (6.4)	0 (0.0)
Insomnia	0 (0.0)	1 (2.0)	1 (2.1)	1 (2.3)	2 (4.3)	0 (0.0)
Pharyngitis	2 (3.9)	1 (2.0)	0 (0.0)	2 (4.7)	1 (2.1)	0 (0.0)
Skin papilloma	4 (7.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Clinical Reviewer's OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and SEXVAL = "Male" and SAFFL = "Y" (Placebo-male); TRT01A = "Tralokinumab 150 Q2W" and SEXVAL = "Male" and SAFFL = "Y" (Tralokinumab 150 Q2W-male); TRT01A = "Tralokinumab 300 Q2W" and SEXVAL = "Male" and SAFFL = "Y" (Tralokinumab 300 Q2W-male); TRT01A = "Placebo" and SEXVAL = "Female" and SAFFL = "Y" (Placebo-female); TRT01A = "Tralokinumab 150 Q2W" and SEXVAL = "Female" and SAFFL = "Y" (Tralokinumab 150 Q2W-female); TRT01A = "Tralokinumab 300 Q2W" and SEXVAL = "Female" and SAFFL = "Y" (Tralokinumab 300 Q2W-female); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).
Percent Threshold: Any Column ≥ 4%.
Consistent with Clinical Reviewer's JMP 14.3.0 and JMP Clinical 8.1 analyses.

TEAEs by Race

Figure 13- Bar plot of frequent AEs by PT (17 most frequent PTs in any treatment group in the overall population), by race (White, Black or African American, Asian, Other) - initial treatment period - ECZTRA 6 - safety analysis set



Source: M. 2.7.4 Addendum – Appendix 1, Figure 2.4.15.

Table 35- Summary of Grouped PTs for TEAEs in any subgroup by dose and by race- initial period of ECZTRA 6 trial:

Grouped Term	Placebo-white (N=53) n (%)	Tralokinumab 150 Q2W-white (N=55) n (%)	Tralokinumab 300 Q2W-white (N=56) n (%)	Placebo-asian (N=23) n (%)	Tralokinumab 150 Q2W-asian (N=28) n (%)	Tralokinumab 300 Q2W-asian (N=20) n (%)
Injection site reactions cluster*	1 (1.9)	3 (5.5)	2 (3.6)	0 (0.0)	4 (14.3)	4 (20.0)
Upper respiratory tract infections cluster*	11 (20.8)	16 (29.1)	16 (28.6)	4 (17.4)	9 (32.1)	4 (20.0)
Conjunctivitis cluster*	1 (1.9)	4 (7.3)	2 (3.6)	1 (4.3)	0 (0.0)	1 (5.0)

Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and RACEVAL = "White" and SAFFL = "Y" (Placebo-white); TRT01A = "Tralokinumab 150 Q2W" and RACEVAL = "White" and SAFFL = "Y" (Tralokinumab 150 Q2W-white); TRT01A = "Tralokinumab 300 Q2W" and RACEVAL = "White" and SAFFL = "Y" (Tralokinumab 300 Q2W-white); TRT01A = "Placebo" and RACEVAL = "Asian" and SAFFL = "Y" (Placebo-asian); TRT01A = "Tralokinumab 150 Q2W" and RACEVAL = "Asian" and SAFFL = "Y" (Tralokinumab 150 Q2W-asian); TRT01A = "Tralokinumab 300 Q2W" and RACEVAL = "Asian" and SAFFL = "Y" (Tralokinumab 300 Q2W-asian); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).

Conjunctivitis cluster* includes: Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial.

Injection site reactions cluster* includes: Injection site oedema, Injection site pain, Injection site reaction, Injection site swelling, Injection site urticaria.
Upper respiratory tract infections cluster* includes: Nasopharyngitis, Pharyngitis, Upper respiratory tract infection, Viral upper respiratory tract infection.

Table 36- Continued- Summary of Grouped PTs for TEAEs in any subgroup by dose and by race- initial period of ECZTRA 6 trial:

Grouped Term	Placebo-black (N=11)		Tralokinumab 150 Q2W-black (N=7)		Tralokinumab 300 Q2W-black (N=14)		Placebo-other (N=4)		Tralokinumab 150 Q2W-other (N=6)		Tralokinumab 300 Q2W-other (N=5)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Injection site reactions cluster*	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(16.7)	1	(20.0)
Upper respiratory tract infections cluster*	2	(18.2)	0	(0.0)	1	(7.1)	0	(0.0)	1	(16.7)	0	(0.0)

Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and RACEVAL = "Black or african american" and SAFFL = "Y" (Placebo-black); TRT01A = "Tralokinumab 150 Q2W" and RACEVAL = "Black or african american" and SAFFL = "Y" (Tralokinumab 150 Q2W-black); TRT01A = "Tralokinumab 300 Q2W" and RACEVAL = "Black or african american" and SAFFL = "Y" (Tralokinumab 300 Q2W-black); TRT01A = "Placebo" and RACEVAL = "Other" and SAFFL = "Y" (Placebo-other); TRT01A = "Tralokinumab 150 Q2W" and RACEVAL = "Other" and SAFFL = "Y" (Tralokinumab 150 Q2W-other); TRT01A = "Tralokinumab 300 Q2W" and RACEVAL = "Other" and SAFFL = "Y" (Tralokinumab 300 Q2W-other); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).

Injection site reactions cluster* includes: Injection site pain, Injection site reaction.

Upper respiratory tract infections cluster* includes: Pharyngitis, Upper respiratory tract infection, Viral upper respiratory tract infection.

Table 37 Summary of TEAEs by PT in ≥ 2 (3%) subjects in any subgroup by dose and by race-initial period of ECZTRA 6 trial

Preferred Term	Placebo-white (N=53) n (%)	Tralokinumab 150 Q2W-white (N=55) n (%)	Tralokinumab 300 Q2W-white (N=56) n (%)	Placebo-asian (N=23) n (%)	Tralokinumab 150 Q2W-asian (N=28) n (%)	Tralokinumab 300 Q2W-asian (N=20) n (%)
Viral upper respiratory tract infection	4 (7.5)	12 (21.8)	10 (17.9)	3 (13.0)	6 (21.4)	2 (10.0)
Dermatitis atopic	8 (15.1)	11 (20.0)	5 (8.9)	3 (13.0)	0 (0.0)	2 (10.0)
Upper respiratory tract infection	3 (5.7)	4 (7.3)	7 (12.5)	1 (4.3)	3 (10.7)	2 (10.0)
Dyspepsia	0 (0.0)	3 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	3 (5.7)	3 (5.5)	0 (0.0)	1 (4.3)	1 (3.6)	0 (0.0)
Headache	3 (5.7)	3 (5.5)	4 (7.1)	0 (0.0)	1 (3.6)	1 (5.0)
Bronchitis	0 (0.0)	2 (3.6)	1 (1.8)	0 (0.0)	0 (0.0)	1 (5.0)
Conjunctivitis	0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Conjunctivitis allergic	1 (1.9)	2 (3.6)	1 (1.8)	1 (4.3)	0 (0.0)	1 (5.0)
Cystitis	0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	2 (3.8)	2 (3.6)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)
Ear infection	2 (3.8)	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza	0 (0.0)	2 (3.6)	0 (0.0)	1 (4.3)	0 (0.0)	2 (10.0)
Injection site reaction	0 (0.0)	2 (3.6)	1 (1.8)	0 (0.0)	3 (10.7)	1 (5.0)
Insomnia	1 (1.9)	2 (3.6)	0 (0.0)	0 (0.0)	1 (3.6)	1 (5.0)
Nausea	0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)	1 (3.6)	1 (5.0)
Pharyngitis	3 (5.7)	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinus congestion	1 (1.9)	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and RACEVAL = "White" and SAFFL = "Y" (Placebo-white); TRT01A = "Tralokinumab 150 Q2W" and RACEVAL = "White" and SAFFL = "Y" (Tralokinumab 150 Q2W-white); TRT01A = "Tralokinumab 300 Q2W" and RACEVAL = "White" and SAFFL = "Y" (Tralokinumab 300 Q2W-white); TRT01A = "Placebo" and RACEVAL = "Asian" and SAFFL = "Y" (Placebo-asian); TRT01A = "Tralokinumab 150 Q2W" and RACEVAL = "Asian" and SAFFL = "Y" (Tralokinumab 150 Q2W-asian); TRT01A = "Tralokinumab 300 Q2W" and RACEVAL = "Asian" and SAFFL = "Y" (Tralokinumab 300 Q2W-asian); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).
Percent Threshold: Tralokinumab 150 Q2W-white ≥ 3%.
Consistent with Clinical Reviewer's JMP 14.3.0 and JMP Clinical 8.1 analyses.

Table 38- Continued: Summary of TEAEs by PT in ≥ 2 (3%) subjects in any subgroup by dose and by race- initial period of ECZTRA 6 trial

Preferred Term	Placebo-black (N=11) n (%)	Tralokinumab 150 Q2W-black (N=7) n (%)	Tralokinumab 300 Q2W-black (N=14) n (%)	Placebo-other (N=4) n (%)	Tralokinumab 150 Q2W-other (N=6) n (%)	Tralokinumab 300 Q2W-other (N=5) n (%)
Dermatitis atopic	0 (0.0)	1 (14.3)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)
Eye pruritus	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Herpes ophthalmic	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

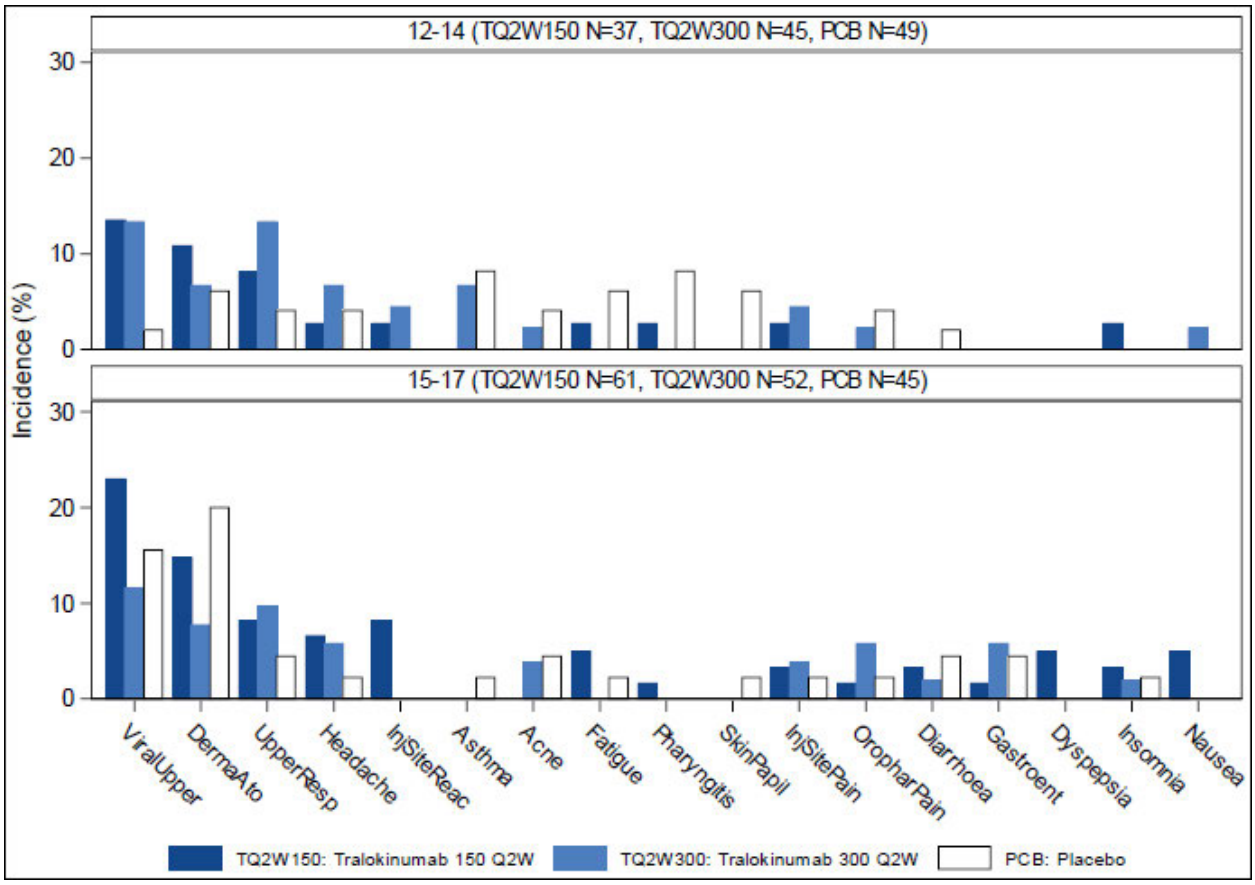
Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and RACEVAL = "Black or african american" and SAFFL = "Y" (Placebo-black); TRT01A = "Tralokinumab 150 Q2W" and RACEVAL = "Black or african american" and SAFFL = "Y" (Tralokinumab 150 Q2W-black); TRT01A = "Tralokinumab 300 Q2W" and RACEVAL = "Black or african american" and SAFFL = "Y" (Tralokinumab 300 Q2W-black); TRT01A = "Placebo" and RACEVAL = "Other" and SAFFL = "Y" (Placebo-other); TRT01A = "Tralokinumab 150 Q2W" and RACEVAL = "Other" and SAFFL = "Y" (Tralokinumab 150 Q2W-other); TRT01A = "Tralokinumab 300 Q2W" and RACEVAL = "Other" and SAFFL = "Y" (Tralokinumab 300 Q2W-other); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).

Percent Threshold: Tralokinumab 150 Q2W-black ≥ 10%. Consistent with Clinical Reviewer's JMP 14.3.0 and JMP Clinical 8.1 analyses.

TEAEs by Age groups (12-14, 15-17 years of age)

Figure 14- Bar plot of frequent AEs by PT (17 most frequent PTs in any treatment group in the overall population), by age group - initial treatment period - ECZTRA 6 - safety analysis set



Source: M. 2.7.4 Addendum – Appendix 1, Figure 2.4.21.

Table 39- Summary of Grouped PTs for TEAEs in any subgroup by dose and by age group-initial period of ECZTRA 6 trial

Grouped Term	Placebo-age 12 to 14 (N=49) n (%)	Tralokinumab 150 Q2W-age 12 to 14 (N=37) n (%)	Tralokinumab 300 Q2W-age 12 to 14 (N=45) n (%)	Placebo-age 15 to 17 (N=45) n (%)	Tralokinumab 150 Q2W-age 15 to 17 (N=61) n (%)	Tralokinumab 300 Q2W-age 15 to 17 (N=52) n (%)
Upper respiratory tract infections cluster*	7 (14.3)	8 (21.6)	11 (24.4)	10 (22.2)	19 (31.1)	11 (21.2)
Injection site reactions cluster*	0 (0.0)	2 (5.4)	4 (8.9)	1 (2.2)	7 (11.5)	3 (5.8)
Conjunctivitis cluster*	1 (2.0)	1 (2.7)	1 (2.2)	1 (2.2)	3 (4.9)	2 (3.8)

Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and AGEGR1 = "12-14" and SAFFL = "Y" (Placebo-age 12 to 14); TRT01A = "Tralokinumab 150 Q2W" and AGEGR1 = "12-14" and SAFFL = "Y" (Tralokinumab 150 Q2W-age 12 to 14); TRT01A = "Tralokinumab 300 Q2W" and AGEGR1 = "12-14" and SAFFL = "Y" (Tralokinumab 300 Q2W-age 12 to 14); TRT01A = "Placebo" and AGEGR1 = "15-17" and SAFFL = "Y" (Placebo-age 15 to 17); TRT01A = "Tralokinumab 150 Q2W" and AGEGR1 = "15-17" and SAFFL = "Y" (Tralokinumab 150 Q2W-age 15 to 17); TRT01A = "Tralokinumab 300 Q2W" and AGEGR1 = "15-17" and SAFFL = "Y" (Tralokinumab 300 Q2W-age 15 to 17); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).

Conjunctivitis cluster* includes: Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial.

Injection site reactions cluster* includes: Injection site oedema, Injection site pain, Injection site reaction, Injection site swelling, Injection site urticaria.

Upper respiratory tract infections cluster* includes: Nasopharyngitis, Pharyngitis, Upper respiratory tract infection, Viral upper respiratory tract infection.

Table 40 Summary of TEAEs by PT in ≥ 2 (3%) subjects in any subgroup by dose and by age group- initial period of ECZTRA 6 trial

Preferred Term	Placebo-age 12 to 14 (N=49) n (%)	Tralokinumab 150 Q2W-age 12 to 14 (N=37) n (%)	Tralokinumab 300 Q2W-age 12 to 14 (N=45) n (%)	Placebo-age 15 to 17 (N=45) n (%)	Tralokinumab 150 Q2W-age 15 to 17 (N=61) n (%)	Tralokinumab 300 Q2W-age 15 to 17 (N=52) n (%)
Viral upper respiratory tract infection	1 (2.0)	5 (13.5)	6 (13.3)	7 (15.6)	14 (23.0)	6 (11.5)
Dermatitis atopic	3 (6.1)	4 (10.8)	3 (6.7)	9 (20.0)	9 (14.8)	4 (7.7)
Injection site reaction	0 (0.0)	1 (2.7)	2 (4.4)	0 (0.0)	5 (8.2)	0 (0.0)
Upper respiratory tract infection	2 (4.1)	3 (8.1)	6 (13.3)	2 (4.4)	5 (8.2)	5 (9.6)
Headache	2 (4.1)	1 (2.7)	3 (6.7)	1 (2.2)	4 (6.6)	3 (5.8)
Dyspepsia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.9)	0 (0.0)
Fatigue	3 (6.1)	1 (2.7)	0 (0.0)	1 (2.2)	3 (4.9)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	3 (4.9)	0 (0.0)
Bronchitis	0 (0.0)	0 (0.0)	2 (4.4)	0 (0.0)	2 (3.3)	0 (0.0)
Conjunctivitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)
Cystitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	1 (1.9)
Diarrhoea	1 (2.0)	0 (0.0)	0 (0.0)	2 (4.4)	2 (3.3)	1 (1.9)
Ear infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)	2 (3.3)	0 (0.0)
Injection site pain	0 (0.0)	1 (2.7)	2 (4.4)	1 (2.2)	2 (3.3)	2 (3.8)
Insomnia	0 (0.0)	1 (2.7)	0 (0.0)	1 (2.2)	2 (3.3)	1 (1.9)
Urticaria	1 (2.0)	0 (0.0)	1 (2.2)	0 (0.0)	2 (3.3)	0 (0.0)
Vomiting	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	1 (1.9)

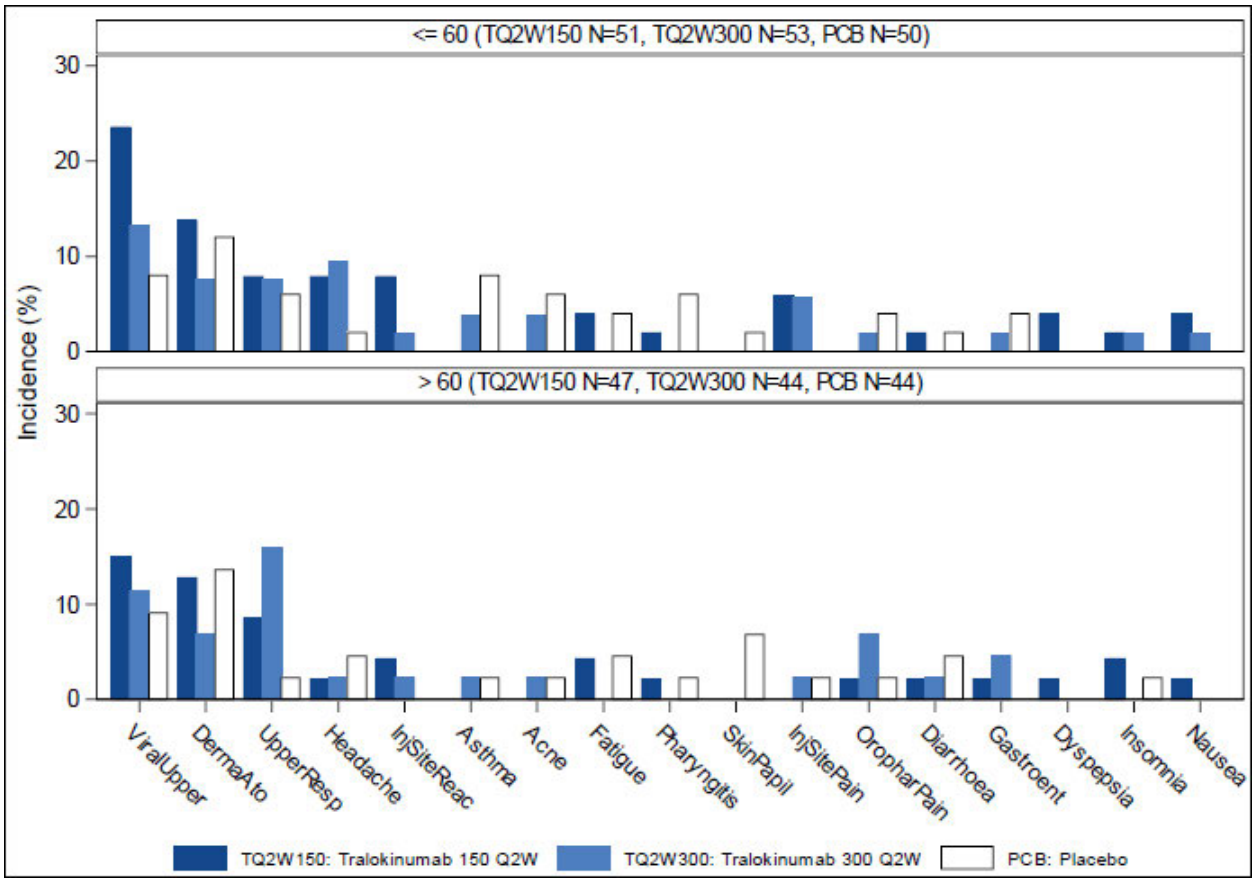
Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and AGEGR1 = "12-14" and SAFFL = "Y" (Placebo-age 12 to 14); TRT01A = "Tralokinumab 150 Q2W" and AGEGR1 = "12-14" and SAFFL = "Y" (Tralokinumab 150 Q2W-age 12 to 14); TRT01A = "Tralokinumab 300 Q2W" and AGEGR1 = "12-14" and SAFFL = "Y" (Tralokinumab 300 Q2W-age 12 to 14); TRT01A = "Placebo" and AGEGR1 = "15-17" and SAFFL = "Y" (Placebo-age 15 to 17); TRT01A = "Tralokinumab 150 Q2W" and AGEGR1 = "15-17" and SAFFL = "Y" (Tralokinumab 150 Q2W-age 15 to 17); TRT01A = "Tralokinumab 300 Q2W" and AGEGR1 = "15-17" and SAFFL = "Y" (Tralokinumab 300 Q2W-age 15 to 17); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).

Percent Threshold: Tralokinumab 150 Q2W-age 15 to 17 ≥ 3%. Consistent with Clinical Reviewer's JMP 14.3.0 and JMP Clinical 8.1 analyses.

TEAEs by Body weight

Figure 15 Bar plot of frequent AEs by PT (17 most frequent PTs in any treatment group in the overall population), by baseline body weight (Kg)- initial treatment period - ECZTRA 6 - safety analysis set



Source: M. 2.7.4 Addendum – Appendix 1, Figure 2.4.27:

Table 41 Summary of TEAEs by PT in ≥ 2 (4%) subjects in any subgroup by dose and by baseline body weight (Kg) group- initial period of ECZTRA 6 trial

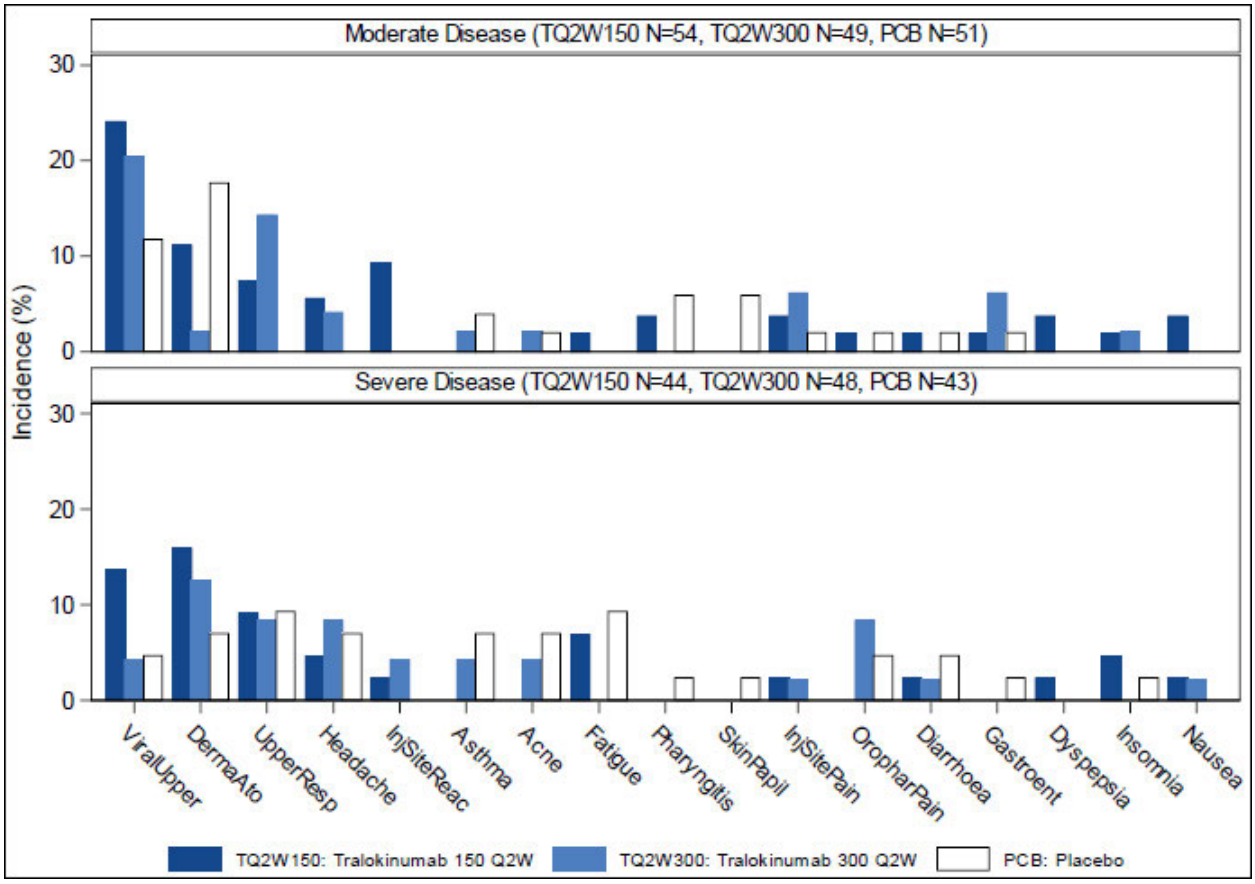
	Placebo		Tralokinumab 150 Q2W		Tralokinumab 300 Q2W		Total	
	<=60 (N=50)	>60 (N=44)	<=60 (N=51)	>60 (N=47)	<=60 (N=53)	>60 (N=44)	<=60 (N=154)	>60 (N=135)
AE in >=2 subjects (4%) by subgroup- initial period- ECZTRA 6								
Viral upper respiratory tract infection	10 (20.0)	11 (25.0)	14 (27.5)	11 (23.4)	16 (30.2)	8 (18.2)	40 (26.0)	30 (22.2)
Dermatitis atopic	10 (20.0)	12 (27.3)	10 (19.6)	10 (21.3)	10 (18.9)	5 (11.4)	30 (19.5)	27 (20.0)
Upper respiratory tract infection	10 (20.0)	5 (11.4)	10 (19.6)	7 (14.9)	6 (11.3)	8 (18.2)	26 (16.9)	20 (14.8)
Headache	2 (4.0)	4 (9.1)	5 (9.8)	2 (4.3)	9 (17.0)	2 (4.5)	16 (10.4)	8 (5.9)
Injection site reaction	2 (4.0)	1 (2.3)	6 (11.8)	3 (6.4)	5 (9.4)	1 (2.3)	13 (8.4)	5 (3.7)
Acne	3 (6.0)	3 (6.8)	1 (2.0)	1 (2.1)	4 (7.5)	1 (2.3)	8 (5.2)	5 (3.7)
Oropharyngeal pain	3 (6.0)	3 (6.8)	1 (2.0)	1 (2.1)	1 (1.9)	4 (9.1)	5 (3.2)	8 (5.9)
Conjunctivitis allergic	0	2 (4.5)	3 (5.9)	2 (4.3)	3 (5.7)	2 (4.5)	6 (3.9)	6 (4.4)
Cough	5 (10.0)	3 (6.8)	1 (2.0)	1 (2.1)	0	2 (4.5)	6 (3.9)	6 (4.4)
Influenza	1 (2.0)	2 (4.5)	4 (7.8)	1 (2.1)	4 (7.5)	0	9 (5.8)	3 (2.2)
Pharyngitis	4 (8.0)	1 (2.3)	2 (3.9)	3 (6.4)	2 (3.8)	0	8 (5.2)	4 (3.0)
Diarrhoea	2 (4.0)	4 (9.1)	1 (2.0)	3 (6.4)	0	1 (2.3)	3 (1.9)	8 (5.9)
Injection site pain	0	2 (4.5)	4 (7.8)	1 (2.1)	3 (5.7)	1 (2.3)	7 (4.5)	4 (3.0)
Asthma	5 (10.0)	1 (2.3)	1 (2.0)	0	2 (3.8)	1 (2.3)	8 (5.2)	2 (1.5)
Fatigue	2 (4.0)	2 (4.5)	2 (3.9)	2 (4.3)	1 (1.9)	0	5 (3.2)	4 (3.0)
Skin infection	0	0	3 (5.9)	1 (2.1)	2 (3.8)	3 (6.8)	5 (3.2)	4 (3.0)
Conjunctivitis	2 (4.0)	2 (4.5)	1 (2.0)	1 (2.1)	1 (1.9)	1 (2.3)	4 (2.6)	4 (3.0)
Gastroenteritis	3 (6.0)	1 (2.3)	0	1 (2.1)	1 (1.9)	2 (4.5)	4 (2.6)	4 (3.0)
Herpes simplex	1 (2.0)	1 (2.3)	1 (2.0)	1 (2.1)	2 (3.8)	2 (4.5)	4 (2.6)	4 (3.0)
Nausea	2 (4.0)	1 (2.3)	2 (3.9)	1 (2.1)	1 (1.9)	1 (2.3)	5 (3.2)	3 (2.2)
Rhinitis allergic	1 (2.0)	1 (2.3)	0	3 (6.4)	2 (3.8)	1 (2.3)	3 (1.9)	5 (3.7)
Urticaria	2 (4.0)	1 (2.3)	2 (3.9)	1 (2.1)	0	2 (4.5)	4 (2.6)	4 (3.0)
Abdominal pain upper	2 (4.0)	2 (4.5)	0	1 (2.1)	1 (1.9)	1 (2.3)	3 (1.9)	4 (3.0)
Bronchitis	0	0	1 (2.0)	2 (4.3)	3 (5.7)	1 (2.3)	4 (2.6)	3 (2.2)
Insomnia	0	1 (2.3)	1 (2.0)	3 (6.4)	2 (3.8)	0	3 (1.9)	4 (3.0)
Oral herpes	1 (2.0)	1 (2.3)	1 (2.0)	0	3 (5.7)	1 (2.3)	5 (3.2)	2 (1.5)
Pyrexia	2 (4.0)	1 (2.3)	2 (3.9)	1 (2.1)	1 (1.9)	0	5 (3.2)	2 (1.5)
Epistaxis	0	3 (6.8)	1 (2.0)	1 (2.1)	1 (1.9)	0	2 (1.3)	4 (3.0)
Folliculitis	1 (2.0)	2 (4.5)	0	2 (4.3)	1 (1.9)	0	2 (1.3)	4 (3.0)
Influenza like illness	2 (4.0)	1 (2.3)	2 (3.9)	1 (2.1)	0	0	4 (2.6)	2 (1.5)
Tonsillitis	1 (2.0)	2 (4.5)	0	1 (2.1)	0	2 (4.5)	1 (0.6)	5 (3.7)
Vomiting	1 (2.0)	1 (2.3)	1 (2.0)	2 (4.3)	1 (1.9)	0	3 (1.9)	3 (2.2)
Constipation	2 (4.0)	0	0	0	3 (5.7)	0	5 (3.2)	0
Ear infection	0	2 (4.5)	0	2 (4.3)	1 (1.9)	0	1 (0.6)	4 (3.0)
Seasonal allergy	1 (2.0)	2 (4.5)	1 (2.0)	0	1 (1.9)	0	3 (1.9)	2 (1.5)
Skin papilloma	1 (2.0)	3 (6.8)	0	0	1 (1.9)	0	2 (1.3)	3 (2.2)

	Placebo		Tralokinumab 150 Q2W		Tralokinumab 300 Q2W		Total	
	<=60 (N=50)	>60 (N=44)	<=60 (N=51)	>60 (N=47)	<=60 (N=53)	>60 (N=44)	<=60 (N=154)	>60 (N=135)
Dizziness	0	1 (2.3)	1 (2.0)	2 (4.3)	0	0	1 (0.6)	3 (2.2)
Gastroenteritis viral	1 (2.0)	2 (4.5)	0	0	0	1 (2.3)	1 (0.6)	3 (2.2)
Inappropriate schedule of drug administration	0	0	1 (2.0)	2 (4.3)	0	1 (2.3)	1 (0.6)	3 (2.2)
Ligament sprain	2 (4.0)	0	1 (2.0)	1 (2.1)	0	0	3 (1.9)	1 (0.7)
Migraine	1 (2.0)	0	3 (5.9)	0	0	0	4 (2.6)	0
Otitis media	1 (2.0)	0	1 (2.0)	2 (4.3)	0	0	2 (1.3)	2 (1.5)
Rhinorrhoea	2 (4.0)	0	1 (2.0)	0	0	1 (2.3)	3 (1.9)	1 (0.7)
Suicidal ideation	0	0	0	1 (2.1)	3 (5.7)	0	3 (1.9)	1 (0.7)
Anaphylactic reaction	0	2 (4.5)	0	1 (2.1)	0	0	0	3 (2.2)
Blood pressure increased	0	0	0	1 (2.1)	0	2 (4.5)	0	3 (2.2)
Dermatitis contact	0	1 (2.3)	0	2 (4.3)	0	0	0	3 (2.2)
Ear pain	1 (2.0)	2 (4.5)	0	0	0	0	1 (0.6)	2 (1.5)
Herpes zoster	2 (4.0)	0	0	1 (2.1)	0	0	2 (1.3)	1 (0.7)
Sinus congestion	1 (2.0)	0	0	2 (4.3)	0	0	1 (0.6)	2 (1.5)
Tooth impacted	0	2 (4.5)	1 (2.0)	0	0	0	1 (0.6)	2 (1.5)
Urinary tract infection	2 (4.0)	0	0	0	1 (1.9)	0	3 (1.9)	0
Eyelid oedema	0	2 (4.5)	0	0	0	0	0	2 (1.5)
Herpes virus infection	0	0	0	0	0	2 (4.5)	0	2 (1.5)
Lice infestation	2 (4.0)	0	0	0	0	0	2 (1.3)	0
Syncope	2 (4.0)	0	0	0	0	0	2 (1.3)	0
Vitamin D deficiency	2 (4.0)	0	0	0	0	0	2 (1.3)	0

Source: Clinical reviewer / OCS Service Desk, OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
AE in >=2 subjects (4%) by subgroup- initial period- ECZTRA 6 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'; Percent Threshold: >= 4%.

TEAEs by Baseline IGA

Figure 16 Bar plot of frequent AEs by PT (17 most frequent PTs in any treatment group in the overall population), by baseline disease severity (IGA score) - initial treatment period - ECZTRA 6 – safety analysis set



Source: M. 2.7.4 Addendum – Appendix 1, Figure 2.4.33

Table 42 Summary of Grouped PTs for TEAEs in any subgroup by dose and by baseline IGA-initial period of ECZTRA 6 trial

Grouped Term	Placebo-IGA 3 (N=51) n (%)	Tralokinumab 150 Q2W- IGA 3 (N=54) n (%)	Tralokinumab 300 Q2W- IGA 3 (N=49) n (%)	Placebo-IGA 4 (N=43) n (%)	Tralokinumab 150 Q2W- IGA 4 (N=44) n (%)	Tralokinumab 300 Q2W- IGA 4 (N=48) n (%)
Upper respiratory tract infections cluster*	9 (17.6)	17 (31.5)	17 (34.7)	8 (18.6)	10 (22.7)	5 (10.4)
Injection site reactions cluster*	1 (2.0)	7 (13.0)	4 (8.2)	0 (0.0)	2 (4.5)	3 (6.3)
Conjunctivitis cluster*	1 (2.0)	3 (5.6)	1 (2.0)	1 (2.3)	1 (2.3)	2 (4.2)

Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and BASEIGA = 3 to 3 and SAFFL = "Y" (Placebo- IGA 3); TRT01A = "Tralokinumab 150 Q2W" and BASEIGA = 3 to 3 and SAFFL = "Y" (Tralokinumab 150 Q2W- IGA 3); TRT01A = "Tralokinumab 300 Q2W" and BASEIGA = 3 to 3 and SAFFL = "Y" (Tralokinumab 300 Q2W- IGA 3); BASEIGA = 4 to 4 and TRT01A = "Placebo" and SAFFL = "Y" (Placebo- IGA 4); BASEIGA = 4 to 4 and TRT01A = "Tralokinumab 150 Q2W" and SAFFL = "Y" (Tralokinumab 150 Q2W- IGA 4); BASEIGA = 4 to 4 and TRT01A = "Tralokinumab 300 Q2W" and SAFFL = "Y" (Tralokinumab 300 Q2W- IGA 4); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).

Conjunctivitis cluster* includes: Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial.

Injection site reactions cluster* includes: Injection site oedema, Injection site pain, Injection site reaction, Injection site swelling, Injection site urticaria.
Upper respiratory tract infections cluster* includes: Nasopharyngitis, Pharyngitis, Upper respiratory tract infection, Viral upper respiratory tract infection.

Table 43 Summary of TEAEs by PT in any subgroup by dose and by baseline IGA- initial period of ECZTRA 6 trial

Preferred Term	Placebo- IGA 3 (N=51) n (%)	Tralokinumab 150 Q2W- IGA 3 (N=54) n (%)	Tralokinumab 300 Q2W- IGA 3 (N=49) n (%)	Placebo- IGA 4 (N=43) n (%)	Tralokinumab 150 Q2W- IGA 4 (N=44) n (%)	Tralokinumab 300 Q2W- IGA 4 (N=48) n (%)
Dermatitis atopic	9 (17.6)	6 (11.1)	1 (2.0)	3 (7.0)	7 (15.9)	6 (12.5)
Viral upper respiratory tract infection	6 (11.8)	13 (24.1)	10 (20.4)	2 (4.7)	6 (13.6)	2 (4.2)
Upper respiratory tract infection	0 (0.0)	4 (7.4)	7 (14.3)	4 (9.3)	4 (9.1)	4 (8.3)
Fatigue	0 (0.0)	1 (1.9)	0 (0.0)	4 (9.3)	3 (6.8)	0 (0.0)
Ear infection	2 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.5)	0 (0.0)
Headache	0 (0.0)	3 (5.6)	2 (4.1)	3 (7.0)	2 (4.5)	4 (8.3)
Insomnia	0 (0.0)	1 (1.9)	1 (2.0)	1 (2.3)	2 (4.5)	0 (0.0)

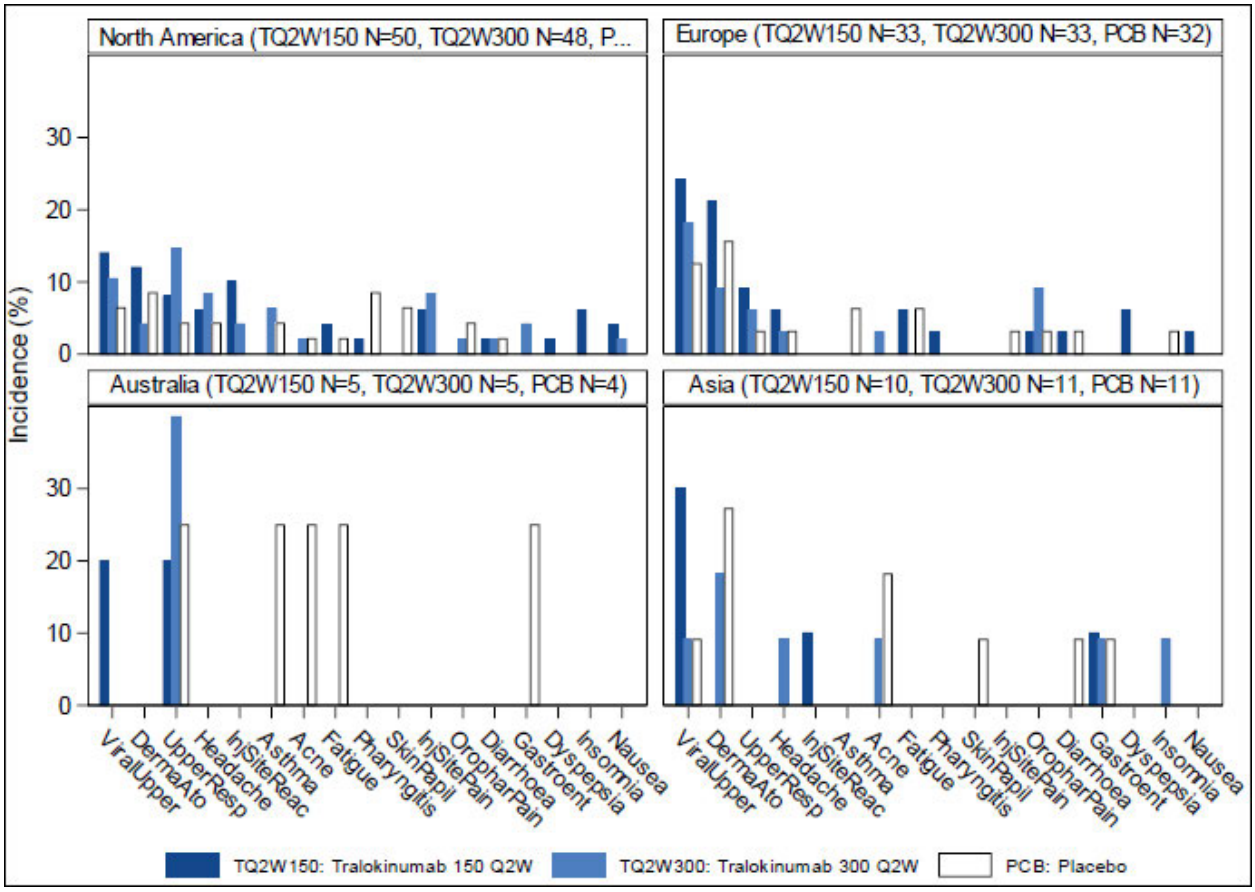
Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and BASEIGA = 3 to 3 and SAFFL = "Y" (Placebo- IGA 3); TRT01A = "Tralokinumab 150 Q2W" and BASEIGA = 3 to 3 and SAFFL = "Y" (Tralokinumab 150 Q2W- IGA 3); TRT01A = "Tralokinumab 300 Q2W" and BASEIGA = 3 to 3 and SAFFL = "Y" (Tralokinumab 300 Q2W- IGA 3); BASEIGA = 4 to 4 and TRT01A = "Placebo" and SAFFL = "Y" (Placebo- IGA 4); BASEIGA = 4 to 4 and TRT01A = "Tralokinumab 150 Q2W" and SAFFL = "Y" (Tralokinumab 150 Q2W- IGA 4); BASEIGA = 4 to 4 and TRT01A = "Tralokinumab 300 Q2W" and SAFFL = "Y" (Tralokinumab 300 Q2W- IGA 4); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).

Percent Threshold: Tralokinumab 150 Q2W- IGA 4 ≥ 4%.

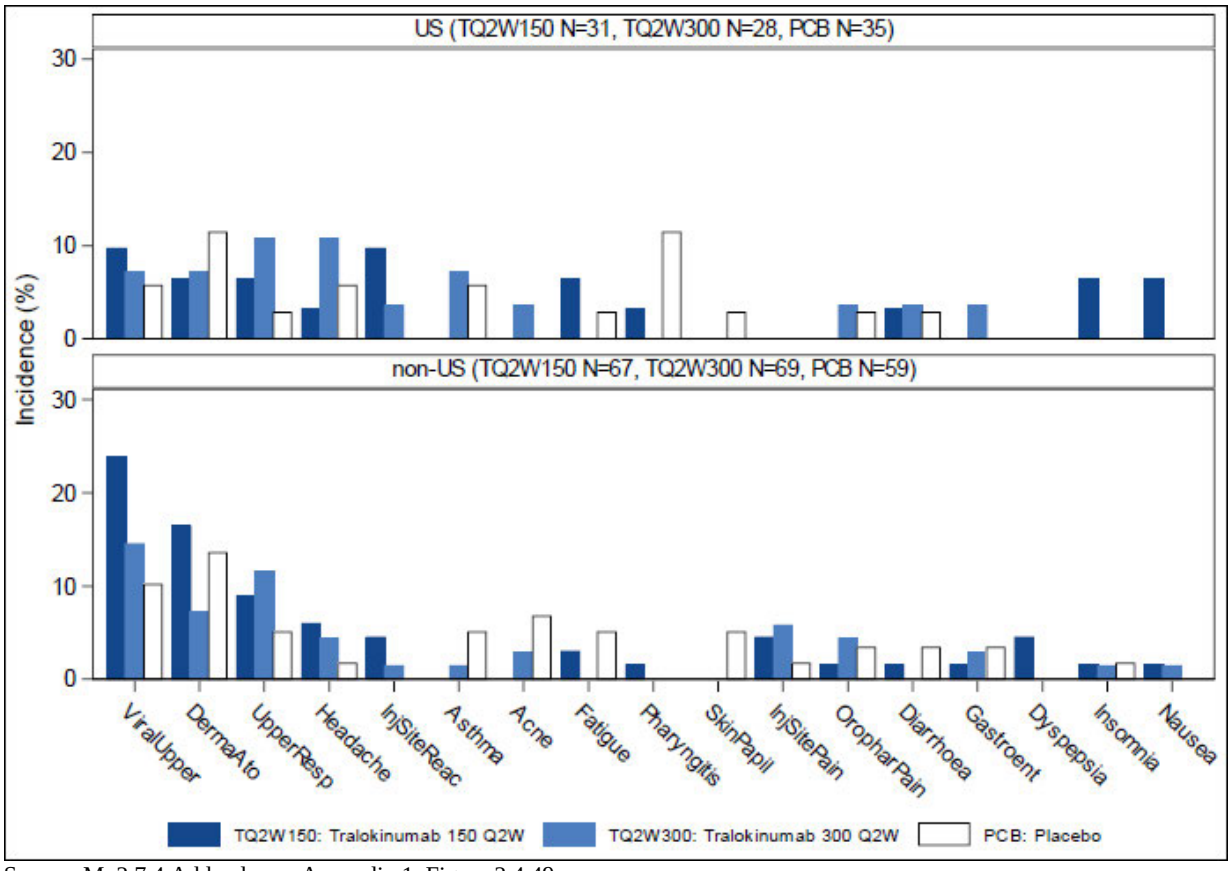
TEAEs by Trial Site Region

Figure 17 Bar plot of frequent AEs by PT (17 most frequent PTs in any treatment group in the overall population), by region (Asia, Australia, Europe or North America) - initial treatment period – ECZTRA 6 - safety analysis set



Source: M. 2.7.4 Addendum – Appendix 1, Figure 2.4.43.

Figure 18 Bar plot of frequent AEs by PT (17 most frequent PTs in any treatment group in the overall population), by region (US and non-US) - initial treatment period - ECZTRA 6 - safety analysis set



Source: M. 2.7.4 Addendum – Appendix 1, Figure 2.4.49.

Table 44 Summary of Grouped PTs for TEAEs in any subgroup by dose and by trial region-initial period of ECZTRA 6 trial

Grouped Term	Placebo-N. America (N=47) n (%)	Tralokinumab 150 Q2W- N. America (N=50) n (%)	Tralokinumab 300 Q2W- N. America (N=48) n (%)	Placebo-Europe (N=32) n (%)	Tralokinumab 150 Q2W-Europe (N=33) n (%)	Tralokinumab 300 Q2W-Europe (N=33) n (%)
Upper respiratory tract infections cluster*	9 (19.1)	11 (22.0)	11 (22.9)	6 (18.8)	11 (33.3)	8 (24.2)
Injection site reactions cluster*	0 (0.0)	8 (16.0)	7 (14.6)	1 (3.1)	0 (0.0)	0 (0.0)
Conjunctivitis cluster*	1 (2.1)	2 (4.0)	1 (2.1)	0 (0.0)	2 (6.1)	0 (0.0)

Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and REGION1 = "North America" and SAFFL = "Y" (Placebo- N. America); TRT01A = "Tralokinumab 150 Q2W" and REGION1 = "North America" and SAFFL = "Y" (Tralokinumab 150 Q2W- N. America); TRT01A = "Tralokinumab 300 Q2W" and REGION1 = "North America" and SAFFL = "Y" (Tralokinumab 300 Q2W- N. America); TRT01A = "Placebo" and REGION1 = "Europe" and SAFFL = "Y" (Placebo-Europe); TRT01A = "Tralokinumab 150 Q2W" and REGION1 = "Europe" and SAFFL = "Y" (Tralokinumab 150 Q2W- Europe); TRT01A = "Tralokinumab 300 Q2W" and REGION1 = "Europe" and SAFFL = "Y" (Tralokinumab 300 Q2W- Europe); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).

Conjunctivitis cluster* includes: Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial.

Injection site reactions cluster* includes: Injection site oedema, Injection site pain, Injection site reaction, Injection site swelling, Injection site urticaria.
Upper respiratory tract infections cluster* includes: Nasopharyngitis, Pharyngitis, Upper respiratory tract infection, Viral upper respiratory tract infection.

Table 45 Continued-Summary of Grouped PTs for TEAEs in any subgroup by dose and by trial region- initial period of ECZTRA 6 trial

Grouped Term	Placebo-Australia (N=4) n (%)	Tralokinumab 150 Q2W-Australia (N=5) n (%)	Tralokinumab 300 Q2W-Australia (N=5) n (%)	Placebo-Asia (N=11) n (%)	Tralokinumab 150 Q2W- Asia (N=10) n (%)	Tralokinumab 300 Q2W- Asia (N=11) n (%)
Conjunctivitis cluster*	0 (0.0)	0 (0.0)	1 (20.0)	1 (9.1)	0 (0.0)	1 (9.1)
Injection site reactions cluster*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)
Upper respiratory tract infections cluster*	1 (25.0)	2 (40.0)	2 (40.0)	1 (9.1)	3 (30.0)	1 (9.1)

Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and REGION1 = "Australia" and SAFFL = "Y" (Placebo- Australia); TRT01A = "Tralokinumab 150 Q2W" and REGION1 = "Australia" and SAFFL = "Y" (Tralokinumab 150 Q2W- Australia); TRT01A = "Tralokinumab 300 Q2W" and REGION1 = "Australia" and SAFFL = "Y" (Tralokinumab 300 Q2W- Australia); TRT01A = "Placebo" and REGION1 = "Asia" and SAFFL = "Y" (Placebo- Asia); TRT01A = "Tralokinumab 150 Q2W" and REGION1 = "Asia" and SAFFL = "Y" (Tralokinumab 150 Q2W- Asia); TRT01A = "Tralokinumab 300 Q2W" and REGION1 = "Asia" and SAFFL = "Y" (Tralokinumab 300 Q2W- Asia); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).

Conjunctivitis cluster* includes: Conjunctivitis allergic.

Injection site reactions cluster* includes: Injection site oedema, Injection site reaction.

Upper respiratory tract infections cluster* includes: Upper respiratory tract infection, Viral upper respiratory tract infection.

Table 46 Summary of TEAEs by PT in ≥ 2 (4%) subjects in any subgroup by dose and by trial region- initial period of ECZTRA 6 trial

Preferred Term	Placebo- N. America (N=47) n (%)	Tralokinumab 150 Q2W- N. America (N=50) n (%)	Tralokinumab 300 Q2W- N. America (N=48) n (%)	Placebo- Europe (N=32) n (%)	Tralokinumab 150 Q2W- Europe (N=33) n (%)	Tralokinumab 300 Q2W- Europe (N=33) n (%)
Viral upper respiratory tract infection	3 (6.4)	7 (14.0)	5 (10.4)	4 (12.5)	8 (24.2)	6 (18.2)
Dermatitis atopic	4 (8.5)	6 (12.0)	2 (4.2)	5 (15.6)	7 (21.2)	3 (9.1)
Injection site reaction	0 (0.0)	5 (10.0)	2 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	2 (4.3)	4 (8.0)	7 (14.6)	1 (3.1)	3 (9.1)	2 (6.1)
Headache	2 (4.3)	3 (6.0)	4 (8.3)	1 (3.1)	2 (6.1)	1 (3.0)
Injection site pain	0 (0.0)	3 (6.0)	4 (8.3)	1 (3.1)	0 (0.0)	0 (0.0)
Insomnia	0 (0.0)	3 (6.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)
Ear infection	0 (0.0)	2 (4.0)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)
Fatigue	1 (2.1)	2 (4.0)	0 (0.0)	2 (6.3)	2 (6.1)	0 (0.0)
Influenza	0 (0.0)	2 (4.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	2 (4.0)	1 (2.1)	0 (0.0)	1 (3.0)	0 (0.0)
Pyrexia	0 (0.0)	2 (4.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)
Sinus congestion	1 (2.1)	2 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin infection	0 (0.0)	2 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urticaria	1 (2.1)	2 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)
Vomiting	0 (0.0)	2 (4.0)	1 (2.1)	1 (3.1)	0 (0.0)	0 (0.0)

Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and REGION1 = "North America" and SAFFL = "Y" (Placebo- N. America); TRT01A = "Tralokinumab 150 Q2W" and REGION1 = "North America" and SAFFL = "Y" (Tralokinumab 150 Q2W- N. America); TRT01A = "Tralokinumab 300 Q2W" and REGION1 = "North America" and SAFFL = "Y" (Tralokinumab 300 Q2W- N. America); TRT01A = "Placebo" and REGION1 = "Europe" and SAFFL = "Y" (Placebo- Europe); TRT01A = "Tralokinumab 150 Q2W" and REGION1 = "Europe" and SAFFL = "Y" (Tralokinumab 150 Q2W- Europe); TRT01A = "Tralokinumab 300 Q2W" and REGION1 = "Europe" and SAFFL = "Y" (Tralokinumab 300 Q2W- Europe); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).

Percent Threshold: Tralokinumab 150 Q2W- N. America ≥ 4%.

Table 47 Continued - Summary of TEAEs by PT in ≥ 2 (4%) subjects in any subgroup by dose and by trial region- initial period of ECZTRA 6 trial

Preferred Term	Placebo-Australia (N=4) n (%)	Tralokinumab 150 Q2W-Australia (N=5) n (%)	Tralokinumab 300 Q2W-Australia (N=5) n (%)	Placebo-Asia (N=11) n (%)	Tralokinumab 150 Q2W- Asia (N=10) n (%)	Tralokinumab 300 Q2W- Asia (N=11) n (%)
Viral upper respiratory tract infection	0 (0.0)	1 (20.0)	0 (0.0)	1 (9.1)	3 (30.0)	1 (9.1)
Astigmatism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)
Gastroenteritis	1 (25.0)	0 (0.0)	0 (0.0)	1 (9.1)	1 (10.0)	1 (9.1)
Injection site oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)
Injection site reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)
Malaise	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)
Upper respiratory tract irritation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)

Source: Clinical Reviewer's analysis by the OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Placebo" and REGION1 = "Australia" and SAFFL = "Y" (Placebo- Australia); TRT01A = "Tralokinumab 150 Q2W" and REGION1 = "Australia" and SAFFL = "Y" (Tralokinumab 150 Q2W- Australia); TRT01A = "Tralokinumab 300 Q2W" and REGION1 = "Australia" and SAFFL = "Y" (Tralokinumab 300 Q2W- Australia); TRT01A = "Placebo" and REGION1 = "Asia" and SAFFL = "Y" (Placebo- Asia); TRT01A = "Tralokinumab 150 Q2W" and REGION1 = "Asia" and SAFFL = "Y" (Tralokinumab 150 Q2W- Asia); TRT01A = "Tralokinumab 300 Q2W" and REGION1 = "Asia" and SAFFL = "Y" (Tralokinumab 300 Q2W- Asia); TRTEMFL = "Y" and APHASE = "INITIAL" (Adverse Events).

Percent Threshold: Tralokinumab 150 Q2W- Asia ≥ 10%.

Reviewer's comment:
The subgroup safety analyses of TEAEs by sex, race, age band, baseline body weight, baseline IGA, and region during the initial period of ECZTRA 6 Trial were not powered for safety analyses. Therefore, no meaningful conclusions may be drawn by comparing the incidence of TEAEs between different treatment Arms within each subgroup (or between different subgroups).

This reviewer agrees with the Applicant's conclusion that safety analyses of the TEAEs did not identify any clinically significant differences between subgroups.

8.2.7. Specific Safety Studies/Clinical Trials

The Applicant did not conduct any specific safety study or clinical trial.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable to this supplement.

Human Reproduction and Pregnancy

No adolescent subjects were reported with pregnancy in trial ECZTRA 6. A 16-year-old female subject who completed trial ECZTRA 6 (ID (b) (6)) was enrolled in the long-term trial ECZTEND (ID (b) (6)) and reported pregnancy (which led to her discontinuation from trial) followed by an elective abortion.

Due to the limited information regarding pregnancy impacts, pregnancy registries were required as postmarketing requirements (PMR 4015-5/-6) at the time of the initial BLA licensure.

Pediatrics and Assessment of Effects on Growth

Not applicable to this supplement.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable to this supplement.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No new safety concerns has been identified from the available postmarketing safety reports.

Expectations on Safety in the Postmarket Setting

There are no safety concerns that are expected to change the favorable risk/benefit assessment or lead to increased risk with administration of ADBRY in the post market setting.

8.2.10. Integrated Assessment of Safety

This efficacy supplement relies on safety data from a single study, ECZTRA 6. Therefore, assessment of safety data from an integrated summary of safety (ISS) is not applicable to the review of this supplement.

120-Day Safety Update

The Applicant did not submit a 120-day safety update report for Trial ECZTRA 6 (conducted from 7/17/2018 to 3/16/2021). The BLA supplement S-001 (submitted under SDN 64 on January 14, 2022) was submitted over 120 days from the data lock date of 5/12/2021 and the final clinical study report date of 8/9/2021 for trial ECZTRA 6.

The Applicant submitted ECZTEND ISS safety update (SDN 64, M. 2.7.4, Appendix 2) for adolescent subjects who had completed ECZTRA 6 and had rolled-over into the LTS Study ECZTEND (with a safety data cutoff date of 3/31/2021). The review team identified no new safety signals in the ECZTEND ISS safety update report.

8.3. Summary and Conclusions

8.3.1. Statistical Issues

There were no major statistical issues affecting overall conclusions. The treatment effects were consistent across endpoints. The amount of missing data was relatively small at Week 16 (i.e., the primary efficacy timepoint). For the tipping point analyses of the IGA 0/1 at Week 16, the tipping point was reached at high imputation of response rate in the placebo group (87%) when testing tralokinumab 300 mg Q2W vs. placebo, which was considered clinically implausible, and was not reached when testing tralokinumab 150 mg Q2W vs. placebo. For the tipping point analyses of EASI-75, the tipping point was not reached for any of the tests of tralokinumab 300 mg Q2W vs. placebo and tralokinumab 150 mg Q2W vs. placebo.

A smaller IGA 0/1 treatment effect was observed in subjects with a baseline IGA score of 4 (severe) compared to baseline IGA score of 3 (moderate) for both tralokinumab doses, mainly attributed to the response rates for the active treatment arms. A smaller EASI-75 treatment effect was also observed for the tralokinumab 150 mg dose in subjects with a baseline IGA score of 4 (severe) compared to baseline IGA score of 3 (moderate); however, the treatment effect for EASI-75 was consistent for the tralokinumab 300 mg dose. For both endpoints, there was some variability in treatment effect across countries; however, this may be due to the relatively small sample sizes in several of the countries.

The statistical reviewer compared the results for efficacy endpoints of IGA 0/1 and EASI-75 at Week 16 between the two pivotal phase 3 trials used to approve tralokinumab for the treatment of moderate to severe AD in adult subjects who are candidates for systemic therapy (Trials ECZTRA 1 and ECZTRA 2), and Trial ECZTRA 6 for adolescent subjects. The treatment effect for the 300 mg dose was similar between adult and adolescent subjects.

8.3.2. Conclusions and Recommendations

Trial ECZTRA 6 achieved statistical significance for both the primary and secondary efficacy endpoints, and the secondary efficacy endpoints were supportive of the primary efficacy

endpoints. In addition, the result for the primary efficacy endpoints in this trial were similar to the results from the previous Phase 3 trials used to approve tralokinumab subcutaneous injections for the treatment of moderate-to-severe AD in adult patients.

The safety data in trial ECZTRA 6 identified no new safety signals and was consistent with the known safety profile of tralokinumab. In the opinion of the Clinical and Statistical review teams, there is sufficient evidence to conclude that the benefits of tralokinumab outweighs its potential risks for the treatment of moderate to severe AD in adolescent subjects. We recommend inclusion of the results of the primary efficacy endpoint (IGA success (score of 0 (clear) or 1 (almost clear) at Week 16), the key secondary efficacy endpoint (EASI75) at week 16, and the secondary efficacy endpoint (Worst pruritus NRS improvement of ≥4-points from baseline to Week 16) in Section 14 of the label. We recommend inclusion of the summary of safety results in Section 6.1 of the ADBRY label.

The determination that 150 mg Q2W dosing can be used safely in the adolescent population cannot be made prior to the goal date and a Complete Response is recommended pending review of the Human Factors information which was submitted late in the review cycle.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not held (for the initial BLA submission, or the S-001 supplement), because no unexpected significant safety/efficacy issue or controversial/ challenging issue was identified that would benefit from discussion at an Advisory Committee meeting.

10 Pediatrics

The Applicant proposes to expand the target population for this indication, treatment of subjects with moderate to severe AD, to include adolescent subjects between 12 to less than 18 years of age. At the time of the initial BLA licensure on 12/27/2021, several post marketing requirements (PMR)s were issued to the Applicant, including PREA PMR 4015-1 for the conduct of trial ECZTRA 6 in adolescent subjects with moderate to severe AD. The results of trial ECZTRA 6 is intended to also fulfil the requirements of PREA PMR 4015-1.

The efficacy supplement (S-001) was presented and discussed at the Pediatric Review Committee (PeRC) meeting on 12/13/2022. The PeRC agreed with the Division's recommendation to reduce the recommended dose for adolescent subjects to an initial dose of 300 mg followed by a maintenance dose of 150 mg every other week.

Sec. 8.4 of the label (Pediatric Use)
The Applicant proposed the following statements for inclusion in Sec 8.4 of the label:

"The safety and effectiveness of ADBRY have been established (b) (4) (b) (4) with moderate-to-severe atopic dermatitis.

Use of ADBRY in this age group is supported by a multicenter, randomized, double-blind, placebo-controlled study (ECZTRA 6) in 289 subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis. The safety and effectiveness were consistent between (b) (4) (b) (4) [see Adverse Reactions (6.1) and Clinical Studies (14)].

Safety and effectiveness (b) (4) (b) (4)"

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The Applicant submitted a proposed Prescribing Information (PI) with the efficacy supplement S-001 on 1/14/2022. The Division (DDD) recommended (b) (4) a dose of 300 mg followed by 150 mg every two weeks, based on similar efficacy and safety data between the two dose groups and higher systemic exposure for the higher dose group.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewer, Madhuri R. Patel, PharmD, in her review of 7/22/2022 found the proposed Prescribing Information (PI) and Patient Package Insert (PPI) acceptable from a medication error perspective.

The following IR was conveyed to the Applicant on 12/19/2022: "We note the proposed dosing regimen for adolescent patients (b) (4) 150 mg every two weeks. However, the currently marketed and proposed user interface is designed around the adult dosing regimen of two injections (150 mg each) for a full dose (300 mg).

> 1. Please provide information on your plan to revise the user interface (e.g., IFU and labeling) to address the two different dosing regimens for the adult and adolescent patient populations.
> 2. Please note, the revisions to the user interface will require additional human factors (HF) information/data. Please provide your high-level HF plan for the revised user interface for our review and feedback".

On 1/5/2023 (SDN 257), the Applicant provided supporting information to the response to the FDA's IR regarding the user interface and human factors information for the 150 mg Q2W dose, to demonstrate that 150 mg Q2W dosing can be used safely in the adolescent population.

However, at the time of this review, DMEPA's evaluation of the adequacy of the HF validation study submitted by the Applicant for the recommended initial dose of 300 mg followed by 150 mg every two weeks in adolescent patients will be considered in a subsequent cycle. Therefore, DDD recommends a Complete Response (CR) for this efficacy supplement (S-001) for this review Cycle.

Due to the planned CR by DDD, OPDP's review of the labeling and the Instructions For Use (IFU) and DMPP's review of the PPI and IFU will be deferred in this review cycle. The final

labeling will reflect the recommendations of all Divisions participating in the labeling review and will be appended to the action letter.

Prescribing information

This application is recommended for Complete Response. Further discussions regarding labeling will not be conducted during this review cycle.

Other Prescription Drug Labeling

This application is recommended for Complete Response. Further discussions regarding labeling will not be conducted during this review cycle.

12 Risk Evaluation and Mitigation Strategies (REMS)

No additional safety concerns were identified, and no REMS were deemed necessary by the review team for this supplemental BLA.

13 Postmarketing Requirements and Commitment

The results of trial ECZTRA 6 is intended to fulfil the requirements of PREA PMR 4015-1. The remaining PMRs issued at the time on the initial BLA licensure on 12/27/2021 remain in effect. There are no new requirements recommended for this supplement.

14 Division Director (DHOT) Comments

NA

15 Division Director (OCP) Comments

NA

16 Division Director (OB) Comments

NA

17 Division Director (Clinical) Comments

NA

18 Office Director (or designated signatory authority) Comments

NA

19 Appendices

19.1. References

References to the literature articles cited were provided as footnotes.

19.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms (FDA Forms 3454 and 3455) in Section 1.3.4 of this sBLA submission for the clinical investigators and sub-investigators who participated in the covered clinical trial. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data.

Prior to Trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4 (a)(3) (i-iv).

The covered clinical trial as defined in 21 CFR 54.2 (e) was Trial LP0162-1334 (ECZTRA 6), which provided the primary data to establish effectiveness and safety of this product in the adolescent target population. Refer to Section 8.1 of this review for the trial design. The Applicant provided the following disclosures for significant payments of other sorts from the Applicant of the covered study [21 CFR 54.4 (a)(3)(ii), 54.2 (f)]:

- (b) (6) received fees > $25,000 USD during the course of the LP0162-1334 trial. (b) (6) received honoraria (b) (4) from LEO Pharma for consulting for Advisory Board.
- (b) (6) received fees > $25,000 USD during the course of the LP0162—1334 trial. (b) (6) received honoraria (b) (4) from LEO Pharma for providing ongoing consultation.
- (b) (6) received > $25,000 for consulting, honorarium and travel related expenses (b) (6) (b) (6) during the course of the LP0162-1334 trial. (b) (6) (b) (6) has received honoraria (b) (4) from LEO Pharma for consulting, honorarium and travel related expenses.

  The Applicant took the following steps to mitigate risk and minimize the potential for bias:

  i. (b) (6) participate in such engagements for multiple sponsors; therefore,

minimizing bias specifically towards LEO Pharma clinical trials.

ii. The contribution of a small number of subjects in each of the Trial sites above is considered small relative to the overall Trial population, thereby reducing a potential bias in the trial outcome.

iii. Trial LP0162-1334 was designed to control for potential biases including implementing a randomization scheme stratified by Trial site, blinded treatment for at least the first 16 weeks of treatment, and dual subject/investigator reported outcomes; all of which aim to reduce the bias of the investigators in favor of the trial drug.

iv. All Tralokinumab trials will be reported in peer-review journals for transparency and reducing risk of reporting bias.

Table 48 Covered Clinical Study: LP0162-1334 (ECZTRA 6)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 94 (PIs)		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
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) 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

19.3. Clinical and Biostatistics

Table 49 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 Protocol for ECZTRA 6, Version 7; page 82

Table 50 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

Note: half-steps (0.5, 1.5, 2.5) are allowed.

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 Protocol for ECZTRA 6, Version 7; pages 83-84

Abbreviations: AS = area score; SS = severity score

Table 51 Results for the Primary and Secondary Endpoints at Week 16 - ECZTRA 6 (RSS; Primary Analysis; Primary Estimand1)

Endpoint	Tralokinumab 300 mg Q2W (N=100)	Tralokinumab 150 mg Q2W (N=99)	Placebo (N=99)
IGA 0/1 (Primary)	20 (20%)	21 (21%)	4 (4%)
Difference from Placebo (95% CI)	16% (8%, 25%)	17.5% (9%, 26%)	-
P-Value	<0.001	<0.001	-
EASI 75	30 (30%)	28 (28%)	4 (7%)
Difference from Placebo (95% CI)	23% (13%, 34%)	22% (11%, 32%)	-
P-Value	<0.001	<0.001	-
Reduction of Adolescent Worst Pruritus NRS of ≥4[2]	24/99 (24%)	22/96 (23%)	4/95 (4%)
Difference from Placebo (95% CI)	20% (11%, 29%)	19% (9%, 28%)	-
P-Value	<0.001	<0.001	-

Source: Statistical Reviewer's Analysis (same as Applicant's analysis); ADIGA.xpt, ADEASI.xpt, ADEDIARY.xpt
[1] Randomized Subjects Set (RSS), defined as all randomized subjects including sites 340 and 341. Subjects who received rescue medication considered non-responders; Subjects with missing data at Week 16 imputed as non-responders
[2] Reduction of Adolescent Worst Daily Pruritus Numeric Rating Scale (NRS) score (weekly average) ≥4 from baseline to Week 16, among subjects with baseline score of ≥4

Table 52 Comparison of Different Approaches for Handling Missing Data – ECZTRA 6 (FAS*)

Different Analyses per Estimand	Tralokinumab 300 mg Q2W (N=97)	Tralokinumab 150 mg Q2W (N=98)	Placebo (N=94)
IGA 0/1 at Week 16			
Primary Estimand:			
Primary Analysis[1]	17 (18%)	21 (21%)	4 (4%)
Difference from Placebo (95% CI)	14% (5%, 22%)	17% (8%, 27%)	-
P-Value	0.002	<0.001	-
Sensitivity Analysis 1[2]	17 (18%)	21 (21%)	4 (4%)
Difference from Placebo (95% CI)	14% (5%, 22%)	17% (8%, 27%)	-
P-Value	0.002	<0.001	-
Sensitivity Analysis 2[3]	17 (18%)	21 (21%)	5 (5%)
Difference from Placebo (95% CI)	13% (4%, 21%)	16% (7%, 26%)	-
P-Value	0.005	<0.001	-
Secondary Estimand:			
Primary Analysis[4]	26%	32%	20%
Difference from Placebo (95% CI)	7% (-9%, 23%)	12% (-4%, 28%)	-
P-Value	0.384	0.125	-
Sensitivity Analysis[5]	26%	31%	20%
Difference from Placebo (95% CI)	7% (-8%, 21%)	12% (-3%, 26%)	-
P-Value	0.365	0.111	-
Tertiary Estimand:			
Sensitivity Analysis[6]	20 (21%)	23 (23%)	5 (5%)
Difference from Placebo (95% CI)	15% (6%, 25%)	18% (9%, 28.0%)	-
P-Value	0.001	<0.001	-
EASI-75 at Week 16			
Primary Estimand:			
Primary Analysis[1]	27 (28%)	28 (29%)	6 (6%)
Difference from Placebo (95% CI)	22% (12%, 32%)	22% (12%, 33%)	-

P-Value	<0.001	<0.001	-
Sensitivity Analysis 1[2]	27 (28%)	28 (29%)	5 (5%)
Difference from Placebo (95% CI)	23% (13%, 33%)	24% (14%, 33%)	-
P-Value	<0.001	<0.001	-
Sensitivity Analysis 2[3]	27 (28%)	28 (29%)	7 (7%)
Difference from Placebo (95% CI)	21% (11%, 31%)	21% (11%, 32%)	-
P-Value	<0.001	<0.001	-
Secondary Estimand:			
Primary Analysis[4]	36%	39%	15%
Difference from Placebo (95% CI)	22% (8%, 36%)	24% (10%, 39%)	-
P-Value	0.003	0.001	-
Sensitivity Analysis[5]	34%	36%	15%
Difference from Placebo (95% CI)	19% (6%, 33%)	21% (7%, 35%)	-
P-Value	0.006	0.003	-
Tertiary Estimand:			
Sensitivity Analysis[6]	36 (37%)	39 (40%)	19 (20%)
Difference from Placebo (95% CI)	17% (5%, 29%)	20% (8%, 33%)	-
P-Value	0.008	0.002	-
Worst Daily Pruritus NRS at Week 16*			
Primary Estimand:			
Primary Analysis[1]	24/96 (25%)	22/95 (23%)	3/90 (3%)
Difference from Placebo (95% CI)	22% (12%, 31%)	20% (11%, 29%)	-
P-Value	<0.001	<0.001	-
Sensitivity Analysis 1[2]	24/96 (25%)	22/95 (23%)	3/90 (3%)
Difference from Placebo (95% CI)	22% (12%, 31%)	20% (11%, 29%)	-
P-Value	<0.001	<0.001	-
Sensitivity Analysis 2[3]	28/96 (29%)	25/95 (26%)	3/90 (3%)
Difference from Placebo (95% CI)	26% (16%, 36%)	23% (13%, 33%)	-
P-Value	<0.001	<0.001	-
Secondary Estimand:			
Primary Analysis[4]	39%	34%	16%
Difference from Placebo (95% CI)	23% (8%, 38%)	19% (4%, 34%)	-
P-Value	0.003	0.015	-
Sensitivity Analysis[5]	35%	33%	16%
Difference from Placebo (95% CI)	20% (6%, 33%)	17% (3%, 32%)	-
P-Value	0.005	0.0165	-
Tertiary Estimand:			
Sensitivity Analysis[6]	32/96 (33%)	30/95 (32%)	16/90 (18%)
Difference from Placebo (95% CI)	16% (3%, 28%)	17% (16%, 19%)	-
P-Value	0.014	<0.001	-

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

*Full Analysis Set (FAS) was defined as all randomized subjects who were dosed with sites 340 and 341 removed.** Reduction of Worst Daily Pruritus NRS score (weekly average) ≥4 from baseline to Week 16, among subjects with baseline score of ≥4

[1] Subjects who received rescue medication considered non-responders. Subjects with missing data at Week 16 imputed as non-responders.

[2] Subjects who permanently discontinued IMP prior to Week 16 considered non-responders.

[3] Missing data at Week 16 imputed using LOCF 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 IMP 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] Missing values at Week 16 imputed as non-responders

Abbreviations: CI, Confidence Interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; IMP, investigational medicinal product; LOCF, last observation carried forward; NRS, numeric rating scale; Q2W, every 2 weeks

Note: Difference, 95% CI and p-value are based on the CMH test stratified by region and baseline IGA score

19.4. Nonclinical Pharmacology/Toxicology

NA

19.5. OCP Appendices (Technical documents supporting OCP recommendations)

Individual Clinical Pharmacology Study Review

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

Tralokinumab serum concentrations, as well as ADA and nAb, were measured using the same validated bioanalytical methods as those described for the previous ECZTRA trials in the initial application.

Briefly, 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.

19.5.2 ECZTRA 6 – Phase 3, Adolescent Subjects with Atopic Dermatitis

Title: Tralokinumab monotherapy for adolescent subjects with moderate-to-severe atopic dermatitis

Objectives: The primary objective was to evaluate the efficacy of SC administration of tralokinumab compared with placebo in treating adolescent subjects (age 12 to <18 years) with moderate-to-severe AD during an initial 16-week treatment period. Secondary objectives include evaluating the efficacy, safety, immunogenicity and tolerability of tralokinumab AD compared with placebo, and evaluating maintenance of effect with continued tralokinumab dosing up to 52 weeks for subjects achieving clinical response at Week 16.

Study population: A total of 294 subjects were planned to initial treatment. 301 subjects were randomized, and 298 subjects received investigational medicinal product (IMP, tralokinumab/placebo). Eventually, the full analysis and safety analysis sets comprised 289 subjects.

Dosing regimen: Tralokinumab 300 mg, tralokinumab 150 mg, or placebo every 2 weeks (Q2W).

Study duration: Initial treatment (which includes the loading dose + initial maintenance dose administered until the primary endpoint) lasted for 16 weeks. Qualified subjects continued into maintenance treatment until week 52.

Methods: Subjects found eligible following the screening period were randomized 1:1:1 to initial treatment with tralokinumab 300 mg, tralokinumab 150 mg, or placebo every 2 weeks (Q2W). Subjects achieving a clinical response (defined as IGA of 0 or 1 [IGA0/1] on a 5-point scale ranging from 0 [clear] to 4 [severe], or at least 75% reduction in Eczema Area and Severity Index [EASI] score from baseline [EASI75]) at Week 16 without the use of rescue treatment from Week 2 to Week 16 continued into maintenance treatment until Week 52 as follows:

• Tralokinumab responders (receiving 300 mg or 150 mg) were re-randomized 1:1 at Week 16 to either tralokinumab Q2W or tralokinumab every 4 weeks (Q4W;), receiving the same dose strength as during the initial treatment period.

• Placebo responders continued to receive placebo Q2W.

Blood samples for pharmacokinetic, pharmacodynamic, and immunogenicity assessments of tralokinumab are summarized in Table 53. Tralokinumab serum concentrations, as well as ADA and nAb, were measured using the same validated bioanalytical methods as those described for the previous ECZTRA trials in the initial application.

Table 53 Sampling time points for the pharmacokinetic, pharmacodynamic, and immunogenicity assessments in ECZTRA 6

Assessment	Treatment period		Safety follow-up period[a] (W52–66)
	Initial (W0–16)	Maintenance / open-label (W16–52)	
In blood			
Tralokinumab serum concentration	W4, W16	W28, W52	W66
Anti-drug antibodies	W0, W4, W16	W28, W52	W66
Blood samples for analysis of: • Serum biomarkers[b] • Whole blood mRNA biomarkers[c]	W0, W16		
Serum IgE	W0, W8, W16	W28, W52	W66
In skin (both lesional and non-lesional)			
Skin tape strip samples[d] for analysis of: • Biomarkers of skin barrier function • Biomarkers of skin inflammation[c]	W0, W8, W16		
Trans-epidermal water loss[c,d]	W0, W16		
Skin swabs for analysis of: • *Staphylococcus aureus* abundance • Skin microbiome[c]	W0, W16		

Abbreviations: CTR = clinical trial report; IgE = immunoglobulin E; W = week number.
Source: Panel 2. Module 2.7.2 Summary of clinical pharmacology addendum

Results:

Demographics:

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

PK analysis:

The geometric mean trough concentrations of tralokinumab over time for the different dosing regimens are demonstrated in Figure 1. For the subjects receiving tralokinumab 150 mg Q2W in the initial treatment period (left side of Figure 1), tralokinumab serum concentrations had reached steady state by Week 16. The geometric mean trough concentration at the previous sampling time point at Week 4 was close to that at Week 16, owing to the initial loading dose

at baseline. For the responders who were re-randomized at Week 16 to maintenance treatment with tralokinumab 150 mg Q2W, the trough concentration remained stable throughout the maintenance period (filled blue squares). For the responders who were re-randomized to Q4W, the trough concentration was approximately halved by the next sampling time point at Week 28 (open green squares), consistent with dose-proportional PK. Conversely, for the tralokinumab 150 mg non-responders who were transferred at Week 16 to open label tralokinumab 300 mg Q2W (open blue circles), the trough concentration was approximately doubled by Week 28 and was similar to the concentrations in the other subjects receiving 300 mg Q2W (right side of the panel). For the subjects receiving tralokinumab 300 mg Q2W in the initial treatment period (right side of Panel 4), the pattern in the initial and maintenance treatment periods was similar to that described above, with trough concentrations approximately the double of those in the corresponding tralokinumab 150 mg groups. A divergence from this expected pattern was the low trough concentration at Week 52 in the tralokinumab 300 mg Q4W group. This result could be due to the small number of subjects.

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

Efficacy responses over time in ECZTRA 6:

As seen in Figure 2, subjects treated with tralokinumab had, on average, a larger reduction in EASI score than subjects treated with placebo. The reduction appeared to be slightly larger for tralokinumab 150 mg than for tralokinumab 300 mg. However, the standard error of the mean for the 2 doses overlapped at most time points. Hence, it cannot be concluded that there was a difference in EASI scores for tralokinumab 150 mg and 300 mg, indicating lack of dose response between the 2 doses. At Week 16, the reduction in EASI score was approximately 40% for placebo-treated subjects and approximately 60% for tralokinumab-treated subjects. As expected, the curve for the total tralokinumab cohort ('Combined' in Panel 2) was between the curves for the 2 tralokinumab dose cohorts.

For IGA, there was a similar trend where approximately 5% of placebo-treated subjects and 22–25% of tralokinumab-treated subjects achieved IGA response at Week 16. The response rate was marginally higher for tralokinumab 150 mg than for tralokinumab 300 mg.

Pharmacodynamic results:

The results for serum biomarkers, markers of skin barrier function, and *S. aureus* colonization in adolescent subjects are consistent with those reported in adults. The serum levels of the key AD disease biomarkers CCL17, IL-22, and IgE decreased in both tralokinumab dose groups relative to the levels in the placebo group during the initial treatment period. Furthermore, there was a general lack of any trend between the 150 mg and 300 mg doses. In both tralokinumab dose groups, the levels of short-chain lipids in lesional skin decreased from baseline to Week 16, and long-chain lipids increased, relative to the levels in the placebo group. Similarly, the level of natural moisturizing factors (filaggrin metabolites) increased in both tralokinumab dose groups. It's of note, these analyses were based on a limited number of subjects (approximately 20–30 per treatment group) from selected trial sites.

Immunogenicity:

The number of ADA-positive subjects in ECZTRA 6 is generally low, which is 7 (7.1%) ADA-positive subjects for tralokinumab 150 mg dose, and no ADA-positive subjects for tralokinumab 300 mg dose. For all subjects with positive ADA status, ADA titers were generally low, ranging from <10–320 in ECZTRA 6, compared to from <10–640 in the ADA ECZTRA (adult pivotal trial) analysis set. Among tralokinumab-treated subjects, 2 (0.7%) subjects in ECZTRA 6 were tested positive for nAb, in comparison with 19 (1.0%) subjects in the ADA ECZTRA analysis set.

The immunogenicity results observed for the adolescent subjects in ECZTRA 6 are comparable with those reported for the adult population. The proportion of subjects with treatment-emergent ADA was marginally higher in ECZTRA 6, including in the placebo group. This may be explained by the small analysis set in ECZTRA 6. ADA titers and the rate of nAb are similarly low in the adolescent and adult trial populations and were deemed not to have an impact on the PK, efficacy, or safety of tralokinumab.

Reviewer's comments:

1. *The tralokinumab PK in adolescent subjects appears to be dose proportional, with an elimination half-life around 22 days, which is consistent with what observed in adults.*
2. *The tralokinumab systemic exposure, geometric mean (%CV) of Ctrough at 105.7 (39.0) and 56.4 (35.4) µg/mL following administration of tralokinumab at 300 mg and 150 mg every other week. The exposure at the 300 mg dose is relatively higher than that in adults (88.4 µg/mL (66.1%, n = 602) in ECZTRA 1; 90.7 µg/mL (59.3%, n = 592) in ECZTRA 2), which may be attributed to the lower mean body weight in adolescents.*

3. *Based on the data from a limited number of subjects, the clinical relevance of the reduction on some investigated serum and skin biomarkers is not fully understood as it was not explored.*
4. *The immunogenicity results observed for the adolescent subjects in ECZTRA 6 are comparable with those reported for the adult population.*

19.5.2. Pharmacometrics (PM) Review

The relationships between dose, plasma concentration, clinical responses and side effects to tralokinumab in adolescent subjects with moderate to severe atopic dermatitis (AD) were investigated as follows:

1) Population pharmacokinetic (popPK) analysis

2) Exposure response and exposure safety analyses

1.1. Data Description:

The PK data for tralokinumab in adolescent subjects are available from 2 completed clinical trials. These trials have been added to the dataset for the updated popPK analysis and are outlined in Table 40 54

Table 54 Overview of adolescent trials added to the updated popPK analysis

Trial ID, link (CTR / PK/bioanalysis report)	Phase, type, duration	Population	Dose, route, regimen (n=exposed subjects)	PK sampling times, number of samples[a]
Trials in adolescent subjects				
CD-RI-CAT-354-1054 M5.3.3.2 CD-RI-CAT-354-1054 CTR	Phase 1 Single dose	Adolescent subjects with asthma	Tralokinumab: 300 mg, SC (n=20)	10 time points: 3 and 8 hours, Days 1, 4, 6, 8, 14, 21, 35, 56 (S=240, S_Q=214)
ECZTRA 6 M5.3.5.1 ECZTRA 6 CTR / Bioanalytical Report 8391820	Phase 3 Multiple dose 52 weeks (26 doses)	Adolescent subjects with atopic dermatitis	Initial treatment Tralokinumab 150 mg (300 mg loading), SC, Q2W (n=99) Tralokinumab 300 mg (600 mg loading), SC, Q2W (n=100) Placebo, SC, Q2W (n=99) Maintenance treatment Tralokinumab responders[b] re-randomised: Tralokinumab 150 mg, SC, Q2W (n=12) Tralokinumab 150 mg, SC, Q4W (n=14) Tralokinumab 300 mg, SC, Q2W (n=11) Tralokinumab 300 mg, SC, Q4W (n=13) Placebo responders[b]: placebo, SC, Q2W (n=6) Non-responders: open-label[c] tralokinumab 300 mg, SC, Q2W (n=234)	5 time points: Weeks 4, 16, 28, 52, 66 (S=1121, S_Q=1024)

[a] Scheduled time points after first dose of tralokinumab; S = total number of samples from all subjects, S_Q = total number of samples within limits of quantification.

[b] Responders in ECZTRA 6 were defined as subjects with clinical response at Week 16, i.e. IGA of 0 or 1 or at least 75% reduction in EASI score from baseline (EASI75), without any use of rescue medication after Week 2.

[c] The open-label arm in ECZTRA 6 included subjects without clinical response[b] at Week 16 from both tralokinumab groups and the placebo group. In addition, subjects in maintenance treatment who met certain criteria of non-responders could transfer to open-label treatment from Week 16. The open-label arm included optional use of mild-to-moderate strength TCS or TCI.

Abbreviations: CTR = clinical trial report; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; PK = pharmacokinetic; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids.

Source: Source: Panel 1. Population pharmacokinetic analysis report addendum

Subjects from the phase 3 study ECZTRA 6, who completed initial treatment (up to Week 16) with a quantifiable serum concentration measurement at Week 16 and had non-missing efficacy responses (IGA and EASI75) at Week 16 and safety measurements (conjunctivitis or upper respiratory tract infections) throughout initial treatment were included for the exposure efficacy and exposure safety analyses, respectively.

1.2. Administration of tralokinumab:

In the Phase 3 study ECZTRA 6, after a loading dosage, adolescent participants received the initial tralokinumab treatment at 300 mg, tralokinumab 150 mg, or placebo every 2 weeks (Q2W) for 16 weeks. Subjects achieving a clinical response at Week 16 without use of rescue treatment continued into maintenance treatment until Week 52: 1). Tralokinumab responders (receiving 300 mg or 150 mg) were re-randomized 1:1 at Week 16 to either tralokinumab Q2W or Q4W; Placebo responders continued to receive placebo Q2W.

1.3. PK Sample Collection:

In the Phase 3 study ECZTRA 6, a total of 1024 quantifiable sparse PK samples collected at Weeks 4, 16, 28, 52 and 66 visits throughout the initial and maintenance treatments in adolescent participants with AD were included in the popPK analysis.

2. PopPK Analysis

2.1. Objectives:

• To quantitatively characterize the PK of tralokinumab in adolescent subjects with AD using non-linear mixed effect analysis.
• To identify sources of variability in the population(s) using covariate analysis.

2.2. Methods:

A previous popPK analysis of tralokinumab included data collected from 10 clinical trials in adult subjects. This updated analysis includes an additional 2 trials in adolescent subjects: a phase 1 trial with a single dose of tralokinumab in subjects with asthma (CD-RI-CAT-354-1054) and a phase 3 trial with multiple doses of tralokinumab in subjects with AD (ECZTRA 6). The combined dataset included 14,585 serum concentrations of tralokinumab from 2,857 subjects.

Population PK (PopPK) modelling of tralokinumab was performed using a non-linear mixed effect modelling approach in NONMEM 7.4. The impact of intrinsic and extrinsic covariates on PK parameters were investigated using an automated stepwise covariate modelling (SCM) approach with forward selection (P<0.01) and backward exclusion (P<0.001). Subsequently, all covariates found to be statistically significant during the SCM approach were evaluated for clinical relevance using a defined set of criteria. The following covariates considered for the analysis were demographic factors (age, sex, body weight, race, and ethnicity), disease status (healthy, asthma, or AD), disease severity (baseline EASI score), and trial-related factors (concentration of drug formulation and ECZTRA trials versus other ['non-ECZTRA'] trials).
Inter-individual and residual variability
20 Interindividual (IIV) and residual variability models were not changed as in the previous analysis. The model included IIV on CL and Vs and a correlation between them. In addition, an additive and proportional residual error model was implemented.

Covariate model building

21 The covariate model building was repeated for the updated popPK analysis. Inclusion of covariates in the model was evaluated based on statistical significance (SCM approach) and clinical relevance.

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).

2.3. Results:

The input data file consisted of 2,909 subjects and 16,476 serum concentration measurements of tralokinumab (including pre-dose). The qualified dataset consisted of 2,857 subjects and 14,585 serum concentrations (Table 55).

Table 55 Number of subjects included in popPK analysis

Trial population	Trial ID	Number of subjects included
Subjects with atopic dermatitis (AD)	D2213C00001	150
	ECZTRA 1	748
	ECZTRA 2	738
	ECZTRA 3	325
	ECZTRA 5	105
	ECZTRA 6	276
	Total (AD)	**2,342**
Subjects with asthma	MI-CP199	134
	CAT-354-0602	19
	CD-RI-CAT-354-1049	288
	CD-RI-CAT-354-1054	20
	Total (asthma)	**461**
Healthy subjects	CAT-354-0703	30
	MI-CP224	24
	Total (healthy)	**54**
All subjects	Total (all)	**2,857**

Source: Panel 3. Population pharmacokinetic analysis report addendum

The demographics of patients included in the popPK analysis are demonstrated in Table 56 including data from 1624 adults and 285 adolescent participants. The body weight distributions of these participants are illustrated in Figure 6.

Table 56 Demographics of subjects included in popPK analysis

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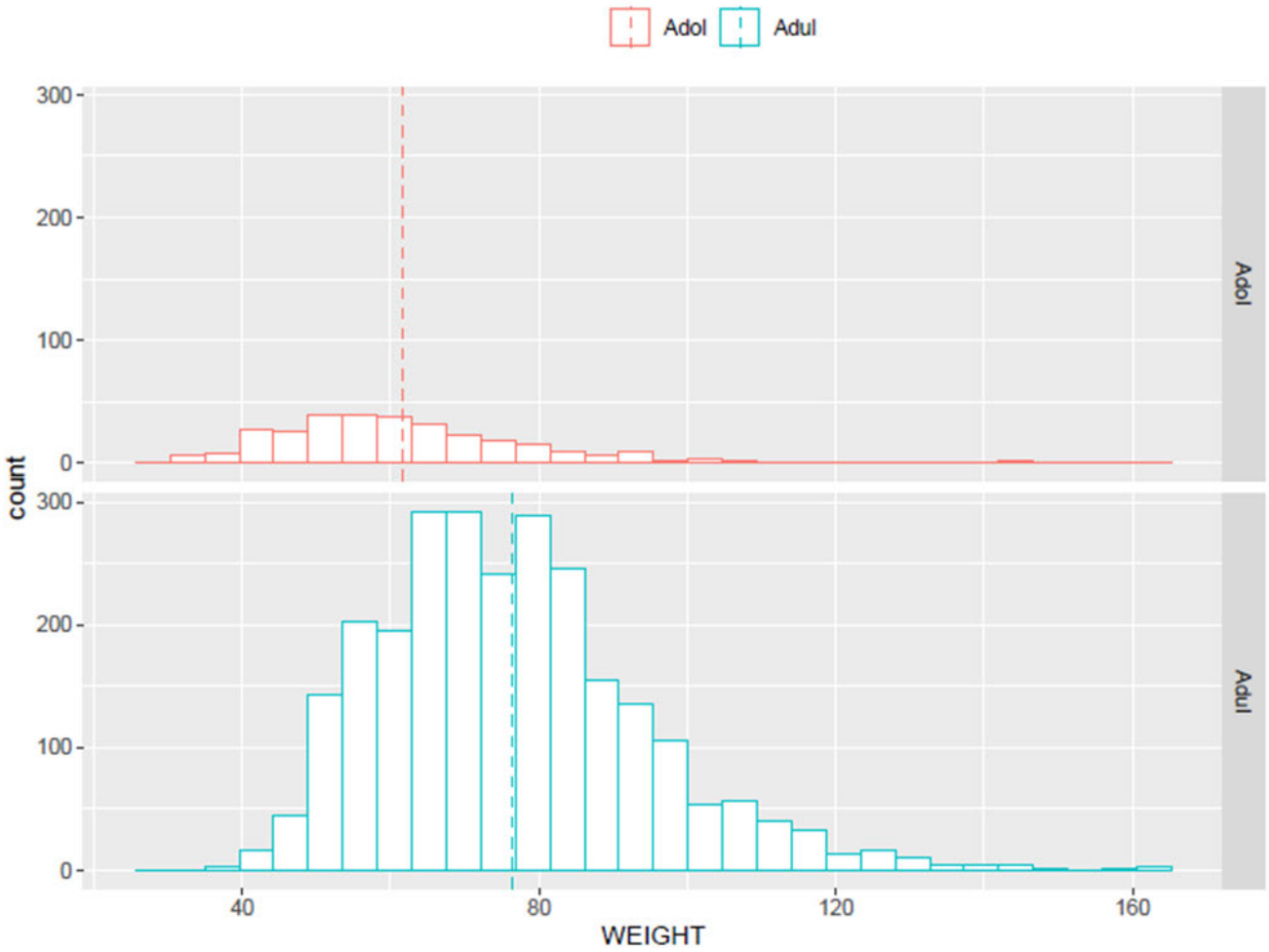
Continuous covariates	N	Mean	SD	Median	Min	Max	Qu25	Qu75
Age (years)	2857	36.88	15.64	35.00	12.00	92.00	24.00	49.00
Body weight (kg)	2857	74.83	18.60	73.00	30.00	165.00	62.00	85.00
Baseline EASI (score)	2342	31.25	13.44	27.60	12.00	72.00	20.40	39.00
eGFR (mL/min)	2857	108.18	21.71	109.14	27.69	182.65	94.25	123.51

Abbreviations: EASI = Eczema Area and Severity Index score (only subjects with atopic dermatitis); eGFR = estimated glomerular filtration rate; N = number of subjects; Qu25/75 = 25th/75th percentile; SD = standard deviation.

Categorical covariates		N
Sex		**2,857**
Female		1,289
Male		1,568
Race		**2,857**
American Indian or Alaska Native		25
Asian		625
Black or African American		214
Native Hawaiian or Other Pacific Islander		10
White		1,901
Other/multiple		82
Ethnicity		**2,857**
Not Hispanic or Latino		2,610
Hispanic or Latino		247
Hepatic impairment		**2,857**
Normal: BILI $\leq ULN_{BILI}$ and AST $\leq ULN_{AST}$ and ALT $\leq ULN_{ALT}$		2,388
Mildly impaired: $1.5 \times ULN_{BILI} \geq$ BILI $\geq ULN_{BILI}$ or AST $> ULN_{AST}$ or ALT $> ULN_{ALT}$		460
Moderately and severely impaired: BILI $> 1.5 \times ULN_{BILI}$		9
Dilution of dose		**2,857**
Diluted	(In the 45 mg dose group of trial D2213C00001, tralokinumab was diluted before subcutaneous administration; see initial M5.3.3.5 PopPK report Section 3.4)	49
Not diluted	(In all other trials with subcutaneous administration, tralokinumab was injected undiluted)	2,808
Disease type		**2,857**
Atopic dermatitis		2,342
Asthma		461
Healthy		54
Trials		**2,857**
ECZTRA (conducted by LEO in subjects with atopic dermatitis)		2,192
Other (conducted by AZ in subjects with asthma or healthy subjects)		665
Age group		**2,857**
Adult		2,561
Adolescent		296

Source: Panel 5. Population pharmacokinetic analysis report addendum

Figure 19 Body weight distribution comparison of adults and adolescent participants



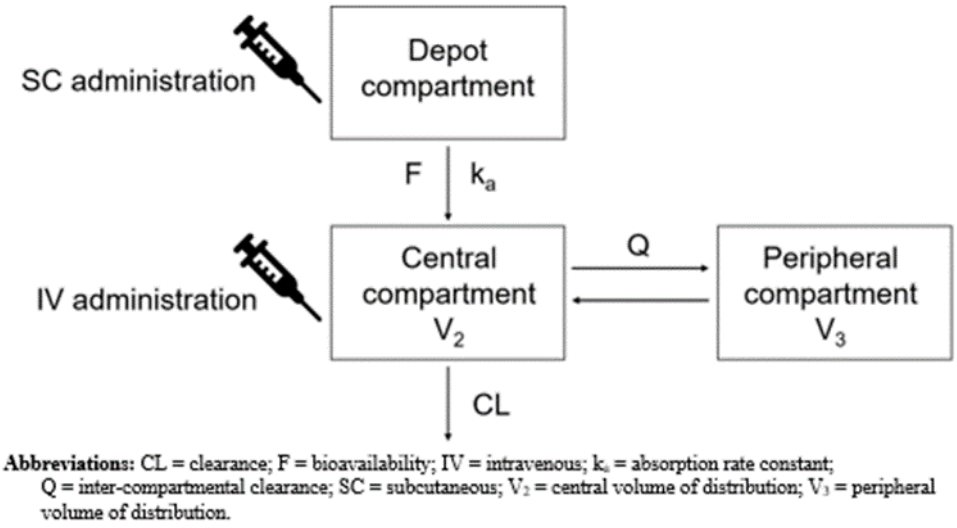
Top: Adolescent body weight distribution from trails ECZTRA 6 (adolescents with AD) and CD-RI-CAT-354-1054 (adolescents with asthma, phase 1 trial). Mean body weight = 61.5 kg.

Bottom: Adult body weight distribution from trails in BLA 761180 (10 clinical trials in adults). Mean body weight = 76.3 kg

Source: Reviewer's independent analysis

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 20). Body weight, non-ECZTRA trials, and concentration of drug formulation were found to be statistically significant and clinically relevant predictors of tralokinumab exposure.

Figure 20 Schematic representation of the PopPK 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.

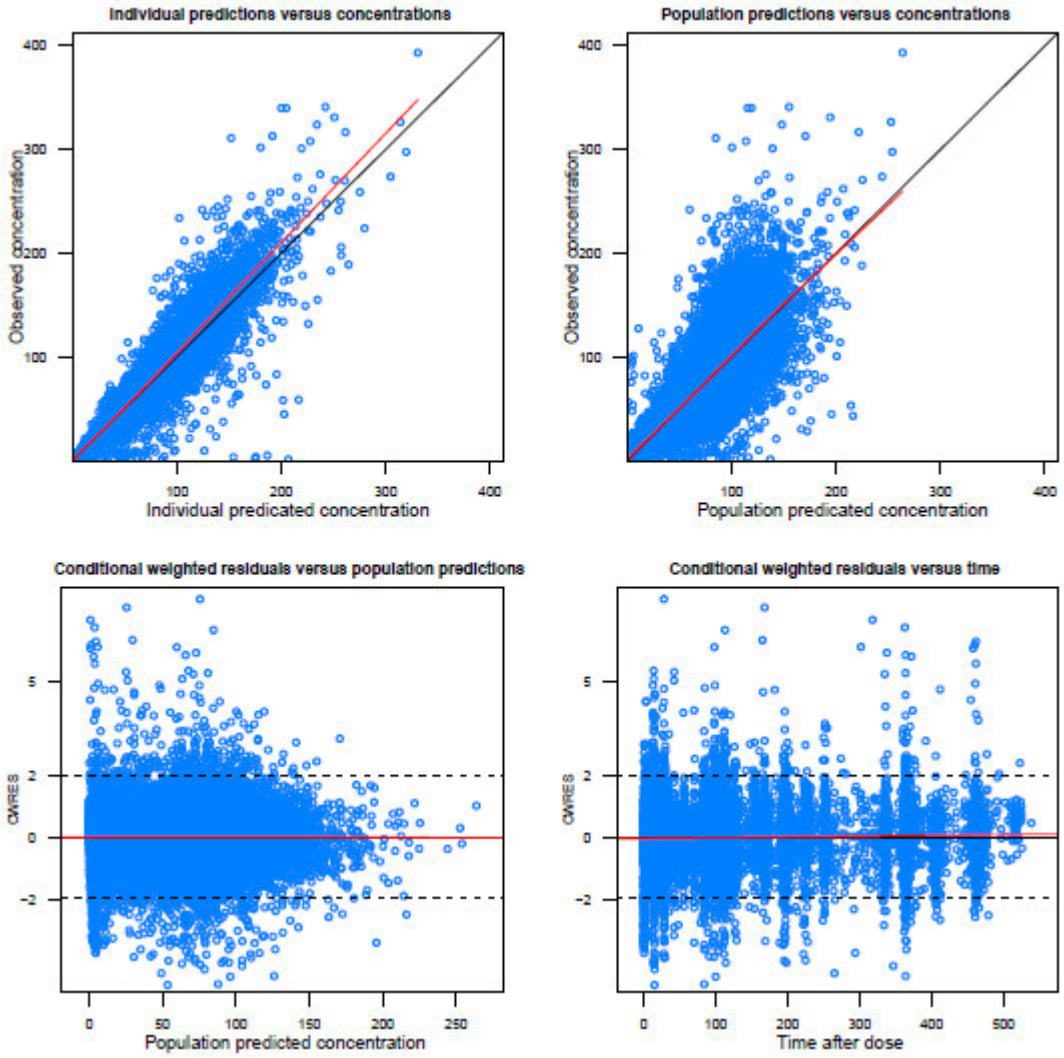
Source: Panel 2. Population pharmacokinetic analysis report addendum

Table 57 Final population PK model PK parameter estimates

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

[a] For continuous covariates, the population estimate is for example: $CL_{population}$ × (covariate/median (covariate))^CL~ $THETA_{covariate}$. For categorical covariates, the estimated parameter in a given category is for example: $CL_{population}$ × (1+ $THETA_{covariate}$). (THETA = fixed effect).
[b] RSE (relative standard error) was obtained from the COVARIANCE option in NONMEM.
[c] IIV (inter-individual variability) was calculated as $\sqrt{(e^{\omega^2}-1)}$.
[d] Correlation was calculated as $\rho_{i,j} = \frac{\omega_{i,j}^2}{\omega_{i,i} \cdot \omega_{j,j}}$.
[e] In the 45 mg dose group of trial D2213C00001, tralokinumab was diluted before subcutaneous administration. In all other trials with subcutaneous administration, tralokinumab was injected undiluted
Source: Panel 9. Population pharmacokinetic analysis report addendum

Figure 21 21 Diagnostic Plots the Final PK Model



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.
The black circles represent the individual observations/predictions/conditional weighted residuals and the red line is the trend line (LOESS).
Source: Reviewer's analysis to confirm Figure 6 in Applicant's Population pharmacokinetic analysis report

2.4. Conclusions

22 A 2-compartment model with linear absorption and elimination kinetics adequately described the PK of tralokinumab in adolescent subject (Table 57 and Figure 21). Body weight

was found to be a clinically relevant predictor of tralokinumab clearance (CL and Q) and volume (V2 and V3) parameters. Non-ECZTRA trials (affecting CL and V2) and concentration of the drug formulation (affecting F and ka) were also found to be clinically relevant predictors of tralokinumab PK parameters. Other covariates (age, eGFR, hepatic impairment, baseline EASI score, sex, race, ethnicity, disease type, and age group) were not identified as clinically relevant predictors of tralokinumab PK. Inter-individual variability was included for CL and V2. The estimated variabilities were moderate, with a CV% of 30.7% for CL and 38.3% for V2.

Reviewer's Comments:

1. *Consistent with what was estimated in adults with AD alone, the updated popPK structural model including adolescent subjects was a 2-compartment model with linear absorption and elimination kinetics and a covariate effect of body weight on volume (V2 and V3) and clearance (CL and Q). Inter-individual variability on PK parameters was moderate.*
2. *Dose-proportional PK was observed, with PK parameters typical of human IgG, suggesting no influence of target-mediated drug disposition.*
3. *The covariate analysis, based on both statistical significance and clinical relevance criteria, identified the same covariates as those identified in the previous analysis in adults. Body weight was found to be a statistically significant and clinically relevant predictor of tralokinumab exposure.*

3. Exposure-Response and Exposure-Safety Analyses

3.1. Objectives

• To investigate the relationship between efficacy and systemic exposure of tralokinumab administered as monotherapy to adolescent subjects with moderate-to-severe AD.

• To investigate the relationship between conjunctivitis or upper respiratory tract infections (identified as adverse drug reactions for tralokinumab) and systemic exposure of tralokinumab in adolescent subjects with moderate-to-severe AD.

3.2. Methods

Data

The exposure-response (ER) analysis set consisted of subjects (Table 58) from ECZTRA 6 who:

- Completed treatment through to Week 16.
- Had a quantifiable serum concentration measurement at Week 16 (only applicable for subjects in the tralokinumab 300 mg and 150 mg Q2W groups)

• Had non-missing efficacy response variables (EASI and IGA) recorded at baseline and Week 16.

Table 58 Number of Subjects from ECZRA 6 included in the Exposure-Response Analysis

	Tralokinumab		Placebo Q2W	Total
	300 mg Q2W	150 mg Q2W		
Number of subjects	84	90	99	273

Abbreviations: Q2W = every 2 weeks.

Source: Panel 1. Module 5.3.4.2 Exposure–response analysis report (Dated August 23, 2022)

Descriptive quantile analyses

In the descriptive quantile analyses, the subjects who received tralokinumab were divided in 4 equally sized groups (quantiles) based on an exposure variable (observed Ctrough at Week 16, or model predicted $AUC_{Week\ 0\text{-}16}$ based on the popPK model incorporating data from adolescents). For each quantile, the given response variable (mean ΔEASI% + standard error of the mean, proportion of IGA responders, or proportion of subjects with conjunctivitis / upper respiratory tract infections) was calculated. For the efficacy variables, this was done for each visit in the initial treatment period (Week 0–16). For conjunctivitis and upper respiratory tract infections, proportion of subjects with each of these adverse drug reactions in the initial treatment period (Week 0–16) within each quantile was reported.

Logistic regression

The exposure-efficacy relationship for the 2 primary endpoints, IGA 0/1 and EASI75 at Week 16, was explored via multi-variate logistic regression models using model-predicted $AUC_{Week\ 0\text{-}16}$ as a factor. Given Ctrough produced similar exposure trend as that based on $AUC_{Week\ 0\text{-}16}$, the $AUC_{Week\ 0\text{-}16}$ derived from the popPK model including data from adolescents was considered the most relevant and representative exposure metric as it reflects the total exposure during the initial treatment period.

As such, $AUC_{Week\ 0\text{-}16}$ was included as a factor in the logistic regression models to investigate the exposure efficacy relationship, rather than imposing a parametric relationship. For both primary endpoints, subjects who received rescue medication after Week 2 as non-responders, and subjects with missing values at Week 16 were also imputed as non-responders. The models were also adjusted for baseline IGA and region factors. Further, the EASI75 model was adjusted for the continuous covariate baseline EASI.

The exposure metric, $AUC_{Week\ 0\text{-}16}$, was divided into 4 exposure levels:

• 0, representing the placebo group.

• [redacted] (b) (6) chosen to split the tralokinumab-treated subjects into 3 equally and sufficiently sized samples.

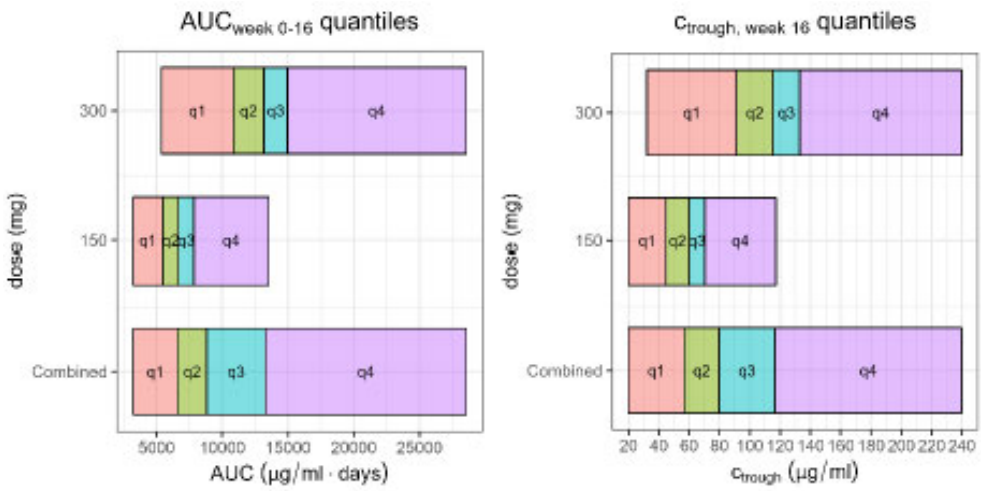
3.3. Results

Descriptive quantile analyses

Exposure-efficacy quantile analysis

In order to investigate tralokinumab exposure and response correlation, the 2 tralokinumab dose groups were divided into quantiles based on exposure in terms of Ctrough at Week 16 and AUC during the entire initial treatment period. Figure 22 shows a graphical overview of the quantiles.

Figure 22 22 Graphical overview of tralokinumab dose group (150 mg, 300 mg, or combined) stratified by quantiles of exposure variables



Source: Panel 3. Module 5.3.4.2 Exposure–response analysis report (Dated August 23, 2022)

For the exposure quantiles (both AUC and Ctrough), the upper and lower bounds are higher for tralokinumab 300 mg than for 150 mg, as expected. Moreover, for the combined dose. The efficacy responses for the tralokinumab 150 mg, 300 mg and two doses combined quantiles are shown in Figures 2, 3 and 4

Overall, in the ECZTRA 6 trial in adolescent subjects, there was a clear treatment effect for tralokinumab versus placebo with regard to reduction in EASI score from baseline to Week 16. The reduction was approximately 40% in placebo-treated subjects and approximately 60% in tralokinumab-treated subjects. There was no marked difference in the reduction in EASI score between the tralokinumab 150 mg and 300 mg dose groups and the 2 groups combined. With regard to IGA response, all results from the quantile analysis are inconclusive.

Exposure-safety quantile analysis

The percentage of adolescent subjects in ECZTRA 6 who had adverse events of conjunctivitis or upper respiratory tract infections are presented in Table 6 for the tralokinumab dose groups and quantiles.

For tralokinumab 150 mg and for the combined dose group, the incidence of conjunctivitis stratified by $AUC_{Week0-16}$ was very low and limited to Q1 and Q2 (Q2 and Q3 for Ctrough 150 mg). For upper respiratory tract infections, the incidence was slightly higher for tralokinumab 150 mg than for placebo. However, there was no tendency of an increase in events with increasing exposure. For tralokinumab 300 mg, no events of conjunctivitis were reported. The incidence of upper respiratory tract infections was similar for tralokinumab 300 mg and placebo. As for tralokinumab 150 mg, there was no tendency of an increase in events with increasing exposure.

In conclusion, the incidence of conjunctivitis and upper respiratory tract infections does not appear to increase with increasing exposure levels.

Logistic regression

The exposure metric, $AUC_{Week\ 0-16}$, was divided into 4 exposure levels:
• 0, representing the placebo group.
• (b) (6) chosen to split the tralokinumab-treated subjects into 3 equally and sufficiently sized samples.

The exposure-efficacy results are shown for IGA 0/1 in Table 3 and for EASI75 in Table 4. For the 3 tralokinumab exposure levels, the distribution of subjects across the 2 dose groups (150 mg and 300 mg) was as expected, e.g., the majority of subjects in the highest exposure group were in the highest dose group.

A clear treatment effect of the exposure to tralokinumab versus placebo was seen on both primary efficacy measures, IGA 0/1 and EASI75. For the subjects receiving tralokinumab, there was no clear correlation between the exposure, as assessed by AUC, and the IGA 0/1 and EASI75 response. For EASI75, there was a tendency towards a higher probability of response in the highest exposure group, although it must be noted that the confidence intervals are wide and overlapping.

Reviewer's Comments:

1. *Due to body weight (BW) was identified as a significant covariate for tralokinumab systemic exposure, bodyweight stratified quantile ER analysis could be confounded by the fact that higher bodyweight subjects getting decreased tralokinumab exposure. Hence, the Applicant conducted BW based descriptive quantile ER is not considered solid.*

2. *In the efficacy exposure-response analyses, conducted on data from the initial 16 weeks of treatment, there was a clear treatment effect for tralokinumab versus placebo. There was no clear correlation of the AUC or Ctrough quantiles and efficacy (EASI or IGA). The lack of positive ER relationship for efficacy was consistent with flat dose response for efficacy between 150 mg and 300 mg Q2W.*
3. *The incidence of conjunctivitis and upper respiratory tract infections does not appear to increase with increasing exposure levels. The ER relationship for conjunctivitis was limited by the low incidence of conjunctivitis event.*

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/s/

HAMID N TABATABAI
02/09/2023 02:53:08 PM
ADBRY for adolescents with AD- Complete Response due to inadequate HF study

DA ZHANG
02/09/2023 03:35:12 PM

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Signing for the primary reviewer Marilena Flouri who is no longer with FDA.

KATHLEEN S FRITSCH on behalf of MOHAMED A ALOSH
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