Amsterdam, 22 May 2025
EMADOC-1700519818-2197482
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Adtralza

Tralokinumab

Procedure no: EMA/PAM/0000258539

Note

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

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1. Introduction

On 10 March 2025, the MAH submitted an interim paediatric study for Adtralza, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that trial LP0162-1335, TRAPEDS 1 is part of a clinical development program.

The paediatric clinical development program for tralokinumab was initiated in parallel with the adult Phase 3 program and includes 3 clinical trials: LP0162-1334 (phase 3 trial in adolescents 12 to <18 years) (including PK modelling to establish the dosing regimen for smaller children), LP0162-1335 (phase 2 PK and safety trial in children 6 to <12 years), and LP0162-1336 (phase 3 confirmatory trial in children 2 to <12 years and infants 6 months to <2 years of age). Furthermore, an open-label, single-arm, phase 3 trial to evaluate the efficacy and safety of tralokinumab administered by a 2 mL prefilled pen in adults and adolescents (12 to 17 years) has been conducted in the US.

2.2. Information on the pharmaceutical formulation used in the study

Licenced formulation.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted an interim report for a single trial:

Type of trial Objectives	Trial ID Trial status	Trial design	Planned number of subjects	Main inclusion criteria and diagnosis	IMPs, dose, route & regimen	Treatment duration	Primary endpoint(s)
Phase 2 PK and safety	TRAPEDS 1 (LP0162-1335) Ongoing	Single (assessor)-blinded, randomised (1:1), parallel-group, with subsequent open-label treatment. Monotherapy	24	Children aged 6 to <12 years with body weight of ≥17 kg at baseline and moderate to severe AD, candidates for systemic treatment: - AD of ≥10% BSA - EASI score ≥16 - IGA score ≥3	Initial treatment *Tralokinumab low dose* - Subjects with body weight 17-<40 kg: 150 mg, SC[a], Q4W, after 300 mg initial loading dose - Subjects with body weight ≥40 kg: 150 mg, SC[a], Q2W, after 300 mg initial loading dose. *Tralokinumab high dose* - Subjects with body weight 17-<40 kg: 150 mg, SC[a], Q2W, after 300 mg initial loading dose - Subjects with body weight ≥40 kg: 300 mg, SC[a], Q2W, after 600 mg initial loading dose. Open-label tralokinumab - 150 mg, SC[a], Q2W for all subjects. Long-term open-label tralokinumab - 150 mg, SC[a], Q2W for all subjects, with possible increase to 300 mg Q2W for subjects with body weight ≥40 kg.	Initial treatment 16 weeks Open-label treatment 52 weeks Long-term open-label extension treatment Up to 106 weeks	- C_{trough} at Week 16. - C_{max} between Week 12-Week 14 for Q2W (Week 12-Week 16 for Q4W).[b] - AUC between Week 12-Week 14 for Q2W (Week 12-Week 16 for Q4W).[b] - t_{max} between Week 12-Week 14 for Q2W (Week 12-Week 16 for Q4W).[b]

2.3.2. Clinical study

Description

Trial ID: LP0162-1335

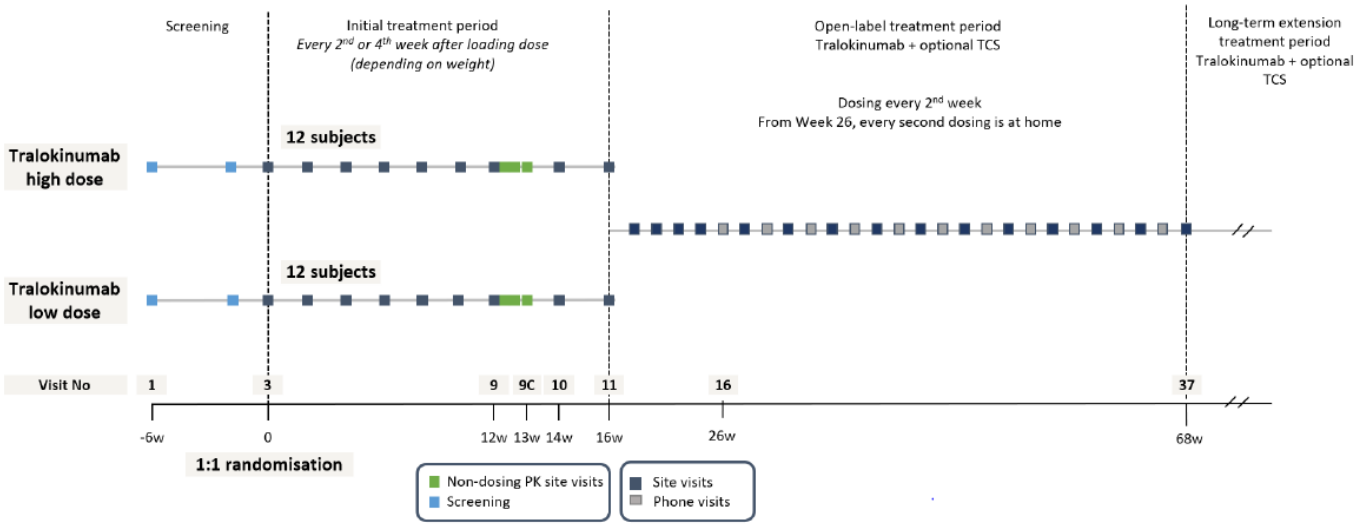
Title: Tralokinumab monotherapy for children with moderate-to-severe atopic dermatitis (TRAPEDS 1)

Methods

This is a single (assessor) blinded, randomised, parallel-group, monotherapy trial to evaluate the pharmacokinetics and safety of tralokinumab in children (aged 6 to <12 years) with moderate to severe AD. The trial consists of a 2- to 6-week screening period, a 16-week initial treatment period where subjects were randomised 1:1 to receive either a low fixed dose, or a high fixed dose of tralokinumab (Week 0 to Week 16), a 52-week open-label treatment period (Week 16 to Week 68) and a long-term extension treatment period for up to 106 weeks (Week 68 to a global end-of-treatment visit, approximately 15-Jan-2026). After treatment completion (i.e. end-of-treatment visit), or discontinuation of trial product, subjects will enter a 14-week off-drug safety follow-up period for assessment of safety and immunogenicity.

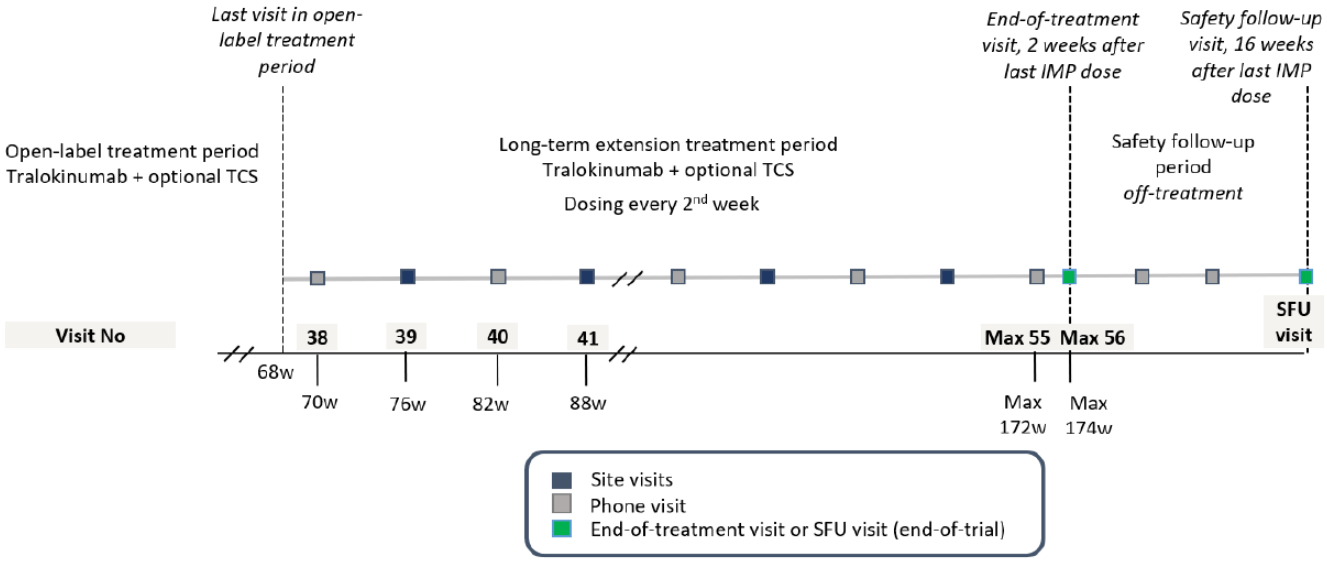
To fulfil the specific measures outlined in the EU agreed Paediatric Investigation Plan and to be able to adhere to the requirements in the paediatric regulation article 46 for submitting results of paediatric trials. This interim CTR presents the results of an interim analysis performed after all subjects had completed the initial and open-label treatment period (i.e. up to Week 68), or the 14-week safety follow-up period for subjects who discontinued the investigational medicinal product (IMP) or withdrew from the trial prior to, or at Week 68. All subjects will be offered to continue in the long-term extension treatment period of this trial.

A. Screening, initial, and open-label treatment periods



Abbreviations: No = number; PK = pharmacokinetic; TCS = topical corticosteroid; w = week.

B. Long-term extension treatment period and safety follow-up period



Abbreviations: IMP = investigatonal medicinal product; no = number; SFU = safety follow-up; TCS = topical corticosteroid; w = week.

Study participants

Diagnosis

Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD.

Main criteria for inclusion

• Age 6 to <12 years.

• Body weight as baseline of ≥ 17 kg.

• History of AD for ≥ 12 months at screening.

• Subjects with documented recent history (within 6 months before screening) of treatment failure to at least mid-strength topical corticosteroids or subjects for whom at least mid-strength topical corticosteroids are medically inadvisable.

• Atopic dermatitis involvement of ≥10% body surface area at screening and baseline according to component A of Scoring Atopic Dermatitis (SCORAD).

• Eczema Area and Severity Index (EASI) ≥16 at the screening and baseline visits.

• An Investigator's Global Assessment (IGA) score of ≥3 at screening and at baseline.

• Subjects must have applied emollient twice daily, or more, for 14 days prior to baseline.

Main criteria for exclusion

• Subjects who have received treatment with any non-marketed drug substance within 3 months or 5 half-lives, whichever is longer, prior to baseline.

• Treatment with topical PDE-4 inhibitors within 2 weeks prior to baseline.

• Treatment with immunomodulatory medications or bleach baths within 4 weeks prior to baseline.

• Use of tanning beds or phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]) within 4 weeks prior to baseline.

• Receipt of live attenuated vaccines within 30 days prior to baseline and during the trial including the safety follow-up period.

• Receipt of any marketed biological therapy or investigational biologic agent e.g. cell-depleting agents or dupilumab within 6 months or 3 months prior to baseline respectively.

• Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis.

• Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD.

• Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antifungals or antiprotozoals within 2 weeks before the baseline visit.

• History of immune complex disease.

• Active or suspected endoparasitic infections, or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization.

• History of past or current tuberculosis or other mycobacterial infection. Evaluation will be according to local guidelines as per local standard of care.

• Established diagnosis of a primary immunodeficiency disorder or secondary immunodeficiency.

Treatments

LEO compound, dose and mode of administration, batch number	
Name and type	Tralokinumab 150 mg/mL solution for injection in pre-filled syringe (brand names: Adtralza® and Adbry®)
Pharmaceutical form	Solution for injection (pre-filled syringe)
Route of administration	Subcutaneous
Unit dose strength	150 mg/mL
Dose level and dose frequency	**Initial treatment period (Week 0 – Week 16):** Subjects were randomized to receive either a low or a high tralokinumab dose regimen: • **Low-dose**: 300 mg loading dose on Day 1 followed by 150 mg tralokinumab every 4 weeks (Q4W) for subjects weighing between 17 - <40 kg at baseline and a 300 mg loading dose on Day 1 followed by 150 mg tralokinumab every 2 weeks (Q2W) for subjects weighing 40 kg or more at baseline. • **High-dose**: 300 mg loading dose on Day 1 followed by 150 mg tralokinumab Q2W for subjects weighing between 17 - <40 kg at baseline and a 600 mg loading dose on Day 1 followed by 300 mg tralokinumab Q2W for subjects weighing 40 kg or more at baseline. **Open-label treatment period (Week 16 – Week 68):** • Open-label treatment with tralokinumab 150 mg Q2W for all subjects. **Long-term extension treatment period (Week 68 to approximately 15-Jan-2026):** • Open-label treatment with tralokinumab 150 mg Q2W. The dose can be increased to 300 mg Q2W for subjects weighing 40 kg or more at the discretion of the investigator.
Batch numbers	Bulk number: 054C20A Packed number: E230178-0001L
Comparator, dose and mode of administration, batch number Not applicable.	
Duration of treatment Up to 68 weeks.	

Objective(s)

Objectives	Endpoints
Primary objective	Primary endpoints (PK parameters)
To establish the PK profile after multiple subcutaneous (SC) administrations of tralokinumab in children with moderate-to-severe AD.	• C_{trough} at Week 16. • C_{max} between Week 12 to Week 14 for Q2W (Week 12 to Week 16 for Q4W). [a] • AUC between Week 12 to Week 14 for Q2W (Week 12 to Week 16 for Q4W). [a] • T_{max} between Week 12 to Week 14 for Q2W (Week 12 to Week 16 for Q4W). [a]
Secondary objectives	Secondary endpoints
To assess the safety and tolerability of multiple SC administrations of tralokinumab in children with moderate-to-severe AD.	• Number of treatment-emergent adverse events in the initial treatment period (Week 0 to Week 16). • Anti-drug antibodies (status) in the initial treatment period (Week 0 to Week 16). • Number of treatment-emergent adverse events in the open-label treatment period (Week 16 to Week 68). • Anti-drug antibodies (status) in the open-label treatment period (Week 16 to Week 68). • Number of treatment-emergent adverse events in the long-term extension treatment period (Week 68 to end-of-treatment visit[b]).[c] • Anti-drug antibodies (status) in the long-term extension treatment period (Week 68 to end-of-treatment visit[b]). [c]
To evaluate the efficacy of tralokinumab on severity and extent of AD, and on patient-reported outcomes, in children with moderate-to-severe AD.	• Change in SCORAD from Week 0 to Week 68. • Change in POEM from Week 0 to Week 68. • Change in EASI from Week 0 to Week 68.
Notes: a) The endpoint was also summarized by dosing interval within the low dose level; b) The end-of-treatment visit is held 2 weeks after end-of-treatment (defined as the date of the last IMP dose for each subject); c) These endpoints are not reported in the present interim CTR (Week 68). **Abbreviations:** AD = atopic dermatitis; AUC = area under the curve; C_{max} = maximum concentration; C_{trough} = trough concentration EASI = Eczema Area and Severity Index; EASI-75 = at least 75% reduction in EASI score; IGA = Investigator's Global Assessment; IGA 0/1 = Investigator's Global Assessment score of 0 (clear) or 1 (almost clear); IMP = investigational medicinal product; PK = pharmacokinetics; POEM = Patient-Oriented Eczema Measure; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; SCORAD = SCORing Atopic Dermatitis; T_{max} = time to maximum concentration.	
Statistical methods Pharmacokinetic and safety parameters are summarized descriptively. Secondary efficacy endpoints are presented as observed.	

Sample size

At least 24 subjects were planned to be randomized.

Randomisation and blinding (masking)

This trial is assessor blinded (efficacy and safety assessments).

Statistical Methods

Pharmacokinetic and safety parameters are summarized descriptively. Secondary efficacy endpoints are presented as observed.

CHMP comment

This is a small phase 2 trial that is part of a paediatric development plan for tralokinumab. The purpose of this trial is to help determine the optimised dose for the subsequent phase 3 pivotal paediatric trial. As such, two different dosing regimens have been employed in this study, based on body weight for the first 16 weeks of the study. The high dose given to patients ≥40kg represents the currently approved adult dose.

While this is an open label study, the assessor is blinded which is supported in order to reduce bias.

Inclusion criteria were similar to those for the pivotal trials in adults, with moderate-to-severe atopic dermatitis defined by Investigator's Global Assessment (IGA) score of ≥3, an Eczema Area and Severity Index (EASI) score of ≥ 16 at baseline and a minimum body surface area (BSA) involvement of ≥ 10% and a previous inadequate response to topical medicinal products (corticosteroids).

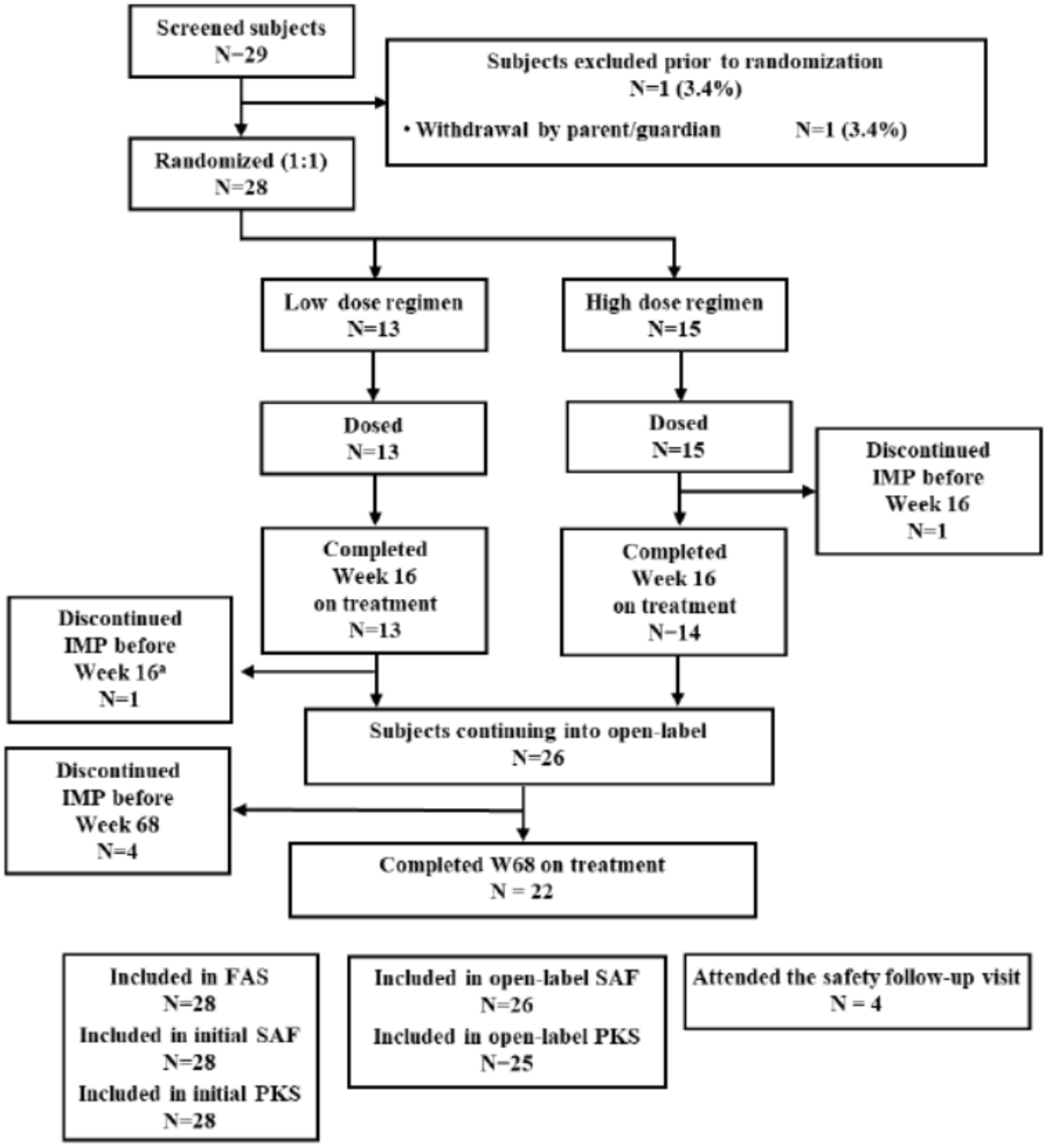
An interim report has been submitted which contains complete PK and efficacy data. The final CSR with final safety data will likely be reviewed in greater detail as part of any future extension of indication variation, together with the phase 3 paediatric data.

Results

Participant flow

The subject disposition is provided in Panel 5.

Panel 5 Disposition of subjects



Notes: a) Last dose of IMP taken at Week 14 after which the subject discontinued IMP. Thus, all doses of IMP were taken during the initial treatment period. The early termination visit was completed within the window of the Week 16 visit, and the subject therefore completed the Week 16 visit on treatment.

Abbreviations: FAS = full analysis set; IMP = investigational medicinal product; N = number of subjects; PKS = pharmacokinetic analysis set; SAF = safety analysis set; W = week.

Baseline data

Subject demographics and baseline characteristics are summarised in the table below. There were no differences between treatment groups in demographics or baseline characteristics that would affect the interpretation of the pharmacokinetic, efficacy, and safety results.

	Low 150 mg Q4W or 150 mg Q2W (N = 13)	High 150 mg Q2W or 300 mg Q2W (N = 15)	Total (N = 28)
Mean (SD) age, years	8.6 (1.5)	8.7 (1.8)	8.7 (1.7)
Age group, n (%)			
Children (2-11 years)	13 (100%)	15 (100%)	28 (100%)
Adolescents (12-17 years)	0	0	0
Adults (≥18 years)	0	0	0
Sex, n (%)			
Male	4 (30.8)	4 (26.7)	8 (28.6)
Female	9 (69.2)	11 (73.3)	20 (71.4)
Race, n (%)			
White	8 (61.5)	10 (66.7)	18 (64.3)
Black or African American	1 (7.7)	-	1 (3.6)
Other	4 (30.8)	5 (33.3)	9 (32.1)
Ethnicity, n (%)			
Hispanic or Latino	2 (15.4)	1 (6.7)	3 (10.7)
Not Hispanic or Latino	11 (84.6)	14 (93.3)	25 (89.3)
Country, n (%)			
Czech Republic	3 (23.1)	2 (13.3)	5 (17.9)
France	1 (7.7)	-	1 (3.6)
Netherlands	3 (23.1)	6 (40.0)	9 (32.1)
Spain	3 (23.1)	2 (13.3)	5 (17.9)
United Kingdom	3 (23.1)	5 (33.3)	8 (28.6)
IGA score, n (%)			
Moderate disease	9 (69.2)	10 (66.7)	19 (67.9)
Severe disease	4 (30.8)	5 (33.3)	9 (32.1)
Mean EASI score (SD)	25.59 (7.28)	28.21 (10.89)	26.99 (9.32)
Mean SCORAD score (SD)	62.72 (14.27)	60.40 (11.39)	61.48 (12.62)
Mean total POEM score (SD)	21.54 (5.21)	20.93 (5.15)	21.21 (5.09)

Abbreviations: EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; N = number of subjects n = number of subjects with observation; POEM = Patient-Oriented Eczema Measure; Q2W = every 2 weeks; Q4W = every 4 weeks; SCORAD = SCORing Atopic Dermatitis; SD = standard deviation.

Number analysed

For this interim CTR, the following analysis sets are in scope:

- Initial PKS (pharmacokinetic analysis set)
- Open-label PKS
- Initial SAF (safety analysis set)
- Open-label SAF
- FAS (full analysis set)

No subjects were excluded from the analysis sets

4 subjects attended the safety follow up visit after permanently discontinuing IMP.

Treatment compliance

For the initial SAF, the overall treatment compliance was high with 27 of the subjects (96.4%) not missing any dose and 1 subject only missing a single dose in the initial treatment period.

The initial PKS is identical to the initial SAF and therefore compliance is not presented separately for this analysis set.

For the open-label SAF, 17 of the subjects (65.4%) had no missed doses, 3 subjects (11.5%) had a single missed dose, 5 subjects (19.2%) had 2 missed doses, and 1 subject had >3 missed doses in the open-label treatment period. For the open-label PKS, 16 of the subjects (64.0%) had no missed doses, 3 subjects (12.0%) had a single missed dose, 5 subjects (20.0%) had 2 missed doses, and 1 subject had >3 missed doses in the open-label treatment period.

Previous AD treatments

Previous AD treatments were as expected for a population with AD. The few differences in use of previous AD treatments observed between treatment groups were not considered to have an impact on the overall interpretation of trial data.

All subjects reported previous use of AD treatment. All subjects reported previous use of TCS, including subjects who reported use of either ultra-high (28.6%) or high (57.1%) potency TCS to treat their AD. Other frequently used previous AD treatments were systemic steroids (28.6% of subjects), TCI (46.4% of subjects), and cyclosporine (10.7% of subjects).

Concomitant medications

The majority of subjects reported use of concomitant medications at baseline (78.6%), in the initial treatment period (92.9%), and in the open-label treatment period (96.2%). In general, the most frequently used concomitant medications were within the categories 'respiratory system' (mostly antihistamines for systemic use) and 'dermatologicals' (mostly 'emollients and protectives' and 'corticosteroids, dermatological preparations').

It should be noted that although TCS and TCI were prohibited in the initial treatment period, the trial design allowed for the use of TCS and TCI prior to and at the time of enrollment in the trial. In this regard, 3 subjects (20%) in the high-dose group (and none in the low-dose group) used TCS and 1 subject in each treatment group used TCI already at baseline.

In the initial treatment period, 'corticosteroids, dermatological preparations' was used by a few more subjects in the high-dose group (11 subjects, 73.3%) than in the low dose group (7 subjects, 53.8%).

CHMP comment:

28 patients were randomised and included in the main analysis sets. Patients were an average of 8.7 years old, mainly female and white. Patients on average had baseline disease characteristics of an EASI score of 26.99, SCORAD score of 61.48 and a POEM score of 21.21.

Treatment compliance was high, particularly in the initial treatment phase (>96%).

Bioanalytical Methods

Bioanalytical report 'Determination of Tralokinumab, Anti-Tralokinumab Antibodies and Neutralizing Anti-Tralokinumab Antibodies in Human Serum Samples from Clinical Study LP0162-1335' was provided with this submission.

CHMP comment:

The bioanalytical report provided with this submission notes the methods used for PK (method ID: 1002979-HAR-IC17-030) and ADA (Method ID: 1002979-HAR-IC20-018) have been previously validated i.e. no new method validations were provided with this application, hence no assessment of the methods was conducted.

For the PK serum concentration method (Gylolab sandwich immunoassay), incurred sample reanalysis (ISR) was performed on 42 samples out of a total of 248. The number of samples used in the incurred samples reanalysis is aligned with ICH M10. The acceptance criteria of 67% of the repeats should have

%difference within 30% for ligand binding assays is aligned with ICH M10, hence acceptable. For the interim analysis for study LP0162-1335, 97.6% of repeat values met the reproducibility criteria. The information on ISR is acceptable and supports the reproducibility of the validated bioanalytical method for study samples. All samples were analyzed within established long-term stability.

For the ADA method (MesoScale Discovery (MSD) bridging assay) there was a total of 7 samples that screened positive of which no samples confirmed positive. Only 24 predose samples were analysed, and none of these screened positive meaning the false positive rate for this study is not within the expected rate for the screening assay (i.e. typically 5%), however as the sample number is very low it is agreed it is difficult to draw reliable conclusions hence no queries are raised.

Additionally, for the 7 positive samples of 151 screening samples (4.6%), these were all confirmed negative in the confirmatory assay. This demonstrates consistently confirmed negative samples, thus helping to mitigate the impact of false positives from the screening assay. Additionally, the screening and confirmatory assays were previously shown to be suitably validated hence there are no concerns regarding the false positive rate of the screening assay.

No NAb analysis has been performed at this interim stage of the study because no ADA samples have confirmed positive so far.

The information provided is acceptable.

PK results

In the initial treatment period, blood samples for PK assessments were collected at Week 4, Week 12, Week 12+3 days, Week 12+5 days, Week 12+7 days, Week 14, and Week 16. In the open-label treatment period, blood samples for PK assessments were collected at Week 28, Week 52, and Week 68.

Finally, blood samples for PK assessments were collected at the safety follow-up visit 14 weeks after the end-of-treatment visit. 4 subjects attended the safety follow up visit after permanently discontinuing IMP. PK data from the safety follow-up visit will be included in listings.

PK parameters for the primary endpoints were assessed using the initial PKS which included 28 subjects who received at least 1 dose of IMP and had at least 1 serum PK observation post-dose. 3 subjects from the high-dose group had non-evaluable PK profiles (i.e. more than 1 missing PK sample); 1 subject (17 –<40 kg) on 150 mg Q2W and 2 subjects (≥40 kg) on 300 mg Q2W.

Tralokinumab is characterized by linear PK. Therefore, it is reasonable to expect that the systemic exposure in the low-dose group would be half of that observed in the high-dose group where the dose is twice as high. However, it should be emphasized that a direct comparison of PK results between the 2 dose groups should be done with caution owing to the difference in the dosing interval (i.e. Q2W versus Q4W). In this regard, it should be noted that the majority of the subjects in the low-dose group had been treated with 150 mg tralokinumab Q4W (N = 10) whereas only a few subjects had been treated with 150 mg tralokinumab Q2W (N = 3). On the other hand, in the high-dose group, all subjects were treated according to the Q2W regimen; either 150 mg Q2W (N = 11) or 300 mg Q2W (N = 4).

The difference in dosing interval between the treatment groups is especially important for the interpretation of the AUC, Ctrough, and Cmax parameters. For the Q4W regimen, the AUC was measured over 4 weeks and was therefore expected to be double that of the Q2W regimen, where the AUC was measured over 2 weeks. Furthermore, owing to the longer Q4W dosing interval, the corresponding Ctrough was expected to be lower than for the Q2W regimen.

Similarly, due to a higher fluctuation with the Q4W compared to the Q2W dosing interval, it is difficult to compare Cmax between treatment groups. Thus, when comparing the PK parameters between the

low- and high-dose groups, the difference in dosing intervals and the fact that the low-dose group is a mixture of Q2W and Q4W dosing intervals should be kept in mind.

Pharmacokinetics results summary

Overall, the PK profile was as expected and was consistent with what has previously been observed with tralokinumab. As expected, the systemic exposure in the low-dose group was approximately half the exposure in the high-dose group. Results for the primary endpoints are summarized by treatment group in Panel 12 and by dose group and weight strata in Panel 13. It should be noted that a direct comparison of PK parameters between the low- and high-dose groups should be done with caution owing to the difference in the dosing interval (i.e. Q2W versus Q4W) between treatment groups.

Panel 12 Summary of primary endpoints – by treatment group - initial PK analysis set

Primary endpoint	Low 150 mg Q4W or 150 mg Q2W (N = 13)	High 150 mg Q2W or 300 mg Q2W (N = 15)
AUC (µg×day/mL)		
n	12	12
Geometric mean (%CV)	1621.48 (41.23)	1664.54 (33.62)
C_{max} (µg/mL)		
n	13	12
Geometric mean (%CV)	102.39 (31.94)	154.45 (35.51)
T_{max} (days)		
n	13	12
Geometric mean (%CV)	3.90 (36.29)	3.33 (24.72)
C_{trough} (µg/mL)		
n	12	12
Geometric mean (%CV)	47.15 (58.38)	105.02 (30.24)

Note: AUC is only calculated in subjects with an evaluable profile, i.e. no more than 1 PK sample missing and both first and last sample in profile present. Observation period for AUC, C_{max} and T_{max} is Week 12 to 14 for Q2W and Week 12 to 16 for Q4W.

Abbreviations: AUC = area under the curve; C_{max} = maximum concentration; C_{trough} = trough concentration at Week 16; CV = coefficient of variation; N = number of subjects in analysis set; n = number of subjects with observation; PK = pharmacokinetic; Q2W = every 2 weeks; Q4W = every 4 weeks; T_{max} = time to maximum concentration.

Panel 13 Summary of primary endpoints – by dose level and weight strata - initial PK analysis set

Primary endpoint	Low 150 mg Q4W or 150 mg Q2W (N = 13)		High 150 mg Q2W or 300 mg Q2W (N = 15)	
	17-<40 kg 150 mg Q4W (N = 10)	≥40 kg 150 mg Q2W (N = 3)	17-<40 kg 150 mg Q2W (N = 11)	≥40 kg 300 mg Q2W (N = 4)
AUC (µg×day/mL)				
n	9	3	10	2
Geometric mean (%CV)	1784.21 (41.53)	1217.05 (25.37)	1697.40 (35.55)	1509.54 (29.69)
C_{max} (µg/mL)				
n	10	3	10	2
Geometric mean (%CV)	100.38 (34.16)	109.37 (28.4)	159.09 (37.14)	133.19 (30.75)
T_{max} (days)				
n	10	3	10	2
Geometric mean (%CV)	3.93 (33.21)	3.83 (55.78)	3.39 (26.87)	3.05 (7.69)
C_{trough} (µg/mL)				
n	9	3	9	3
Geometric mean (%CV)	39.90 (52.44)	77.83 (38.60)	101.52 (33.91)	116.28 (15.97)

Note: AUC is only calculated in subjects with an evaluable profile, i.e. no more than 1 PK sample missing and both first and last sample in profile present. Observation period for AUC, C_{max} and T_{max} is Week 12 to 14 for Q2W and Week 12 to 16 for Q4W.

Abbreviations: AUC = area under the curve; C_{max} = maximum concentration; C_{trough} = trough concentration at Week 16; CV = coefficient of variation; N = number of subjects in analysis set; n = number of subjects with observation; PK = pharmacokinetic; Q2W = every 2 weeks; Q4W = every 4 weeks; T_{max} = time to maximum concentration.

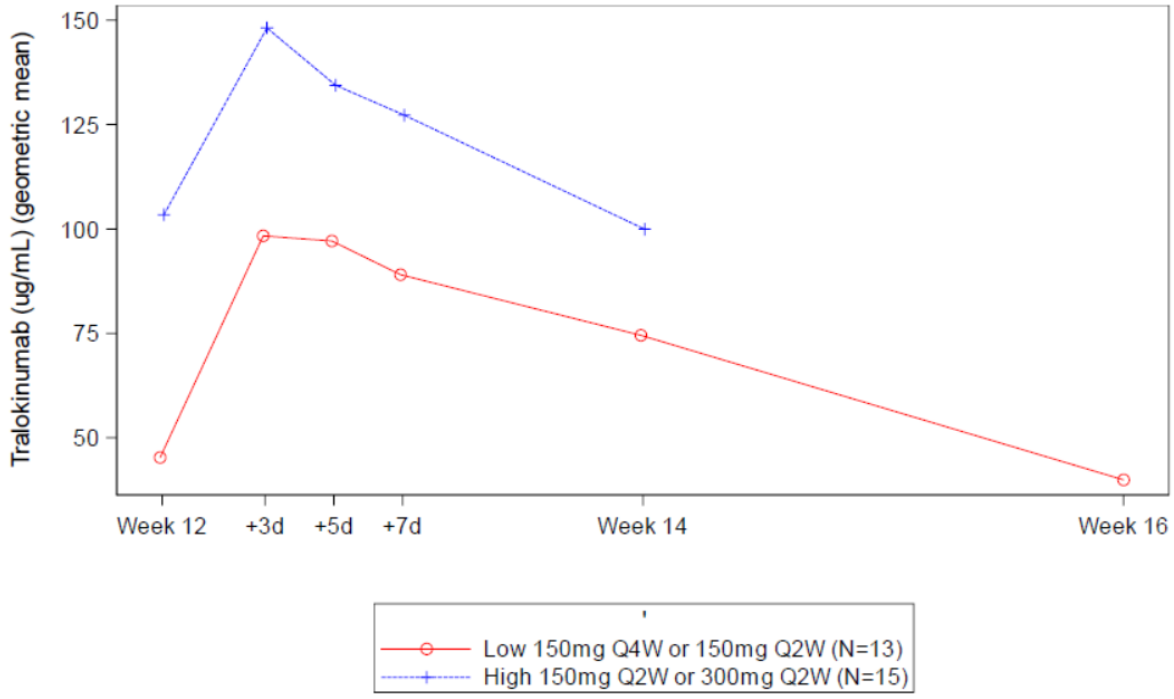
Tralokinumab serum concentrations

Tralokinumab serum concentrations in the initial treatment period are presented graphically in Panel 14. Individual tralokinumab serum concentrations by dose and weight strata are shown in Panel 15.

At Week 16 where steady state is considered to be reached, the geometric mean serum concentration of tralokinumab was 47.15 µg/mL in the low-dose group and 105.02 µg/mL in the high-dose group (Panel 12).

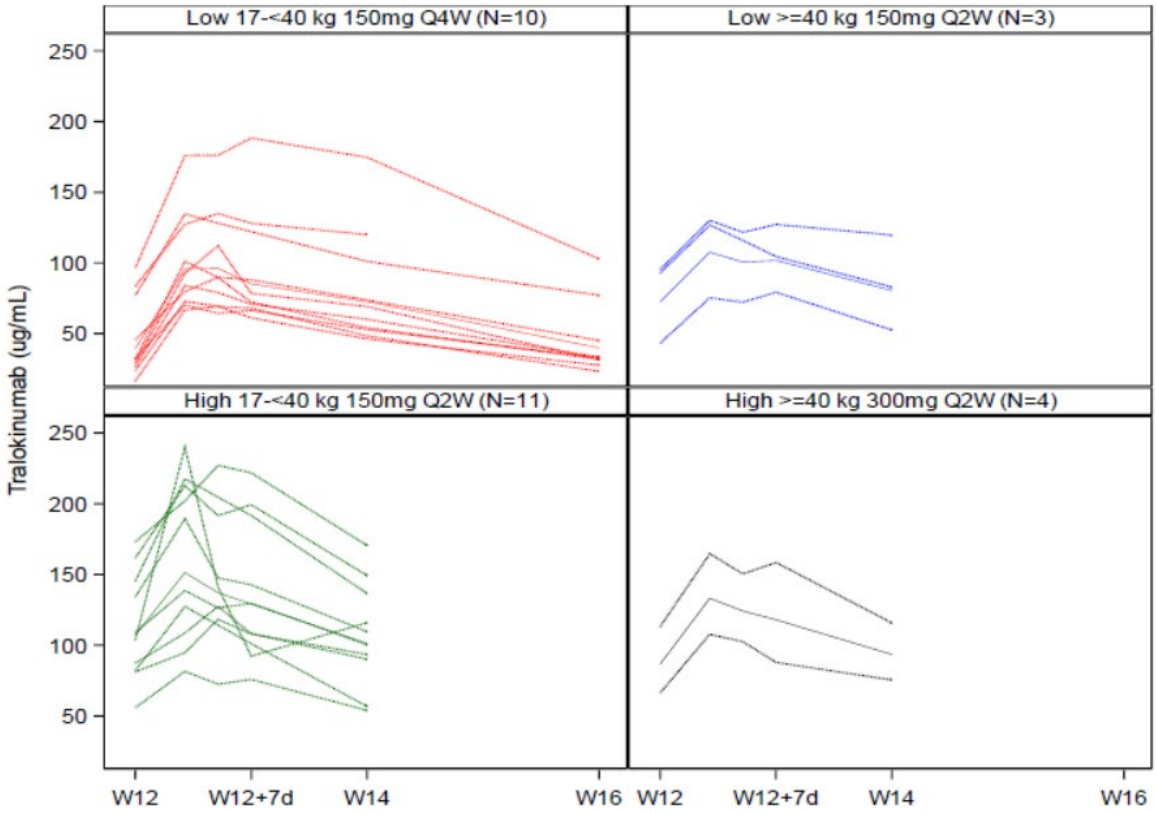
In the open-label treatment period where all subjects had been treated with tralokinumab 150 mg Q2W, the geometric mean serum concentrations were between 80-87 µg/mL).

Panel 14 Tralokinumab serum concentrations by visit - Week 12 to Week 14 (or Week 16 for Q4W dosing) - by dose level - initial PK analysis set



Abbreviations: d: days. N: number of subjects in analysis set. PK: pharmacokinetics. Q2W: every 2 weeks. Q4W: every 4 weeks.
Notes: Observation period for PK profile is Week 12 to 14 for Q2W and Week 12 to 16 for Q4W.

Panel 15 Individual serum concentrations by visit - by dose level and weight strata - initial PK analysis set



Abbreviations: d: days. N: number of subjects in analysis set. PK: pharmacokinetics. Q2W: every 2 weeks. Q4W: every 4 weeks. W: week.
Notes: Solid line shows geometric mean. Dotted lines shows individual concentration. Observation period for PK profile is Week 12 to 14 for Q2W and Week 12 to 16 for Q4W.

CHMP comment:

PK data has been provided which is of limited use due to the different treatment regimens and sampling durations (q2w v q4w) and different doses (150mg v 300mg) involved. In addition, the sample sizes, particularly in the high weight (≥40 kg) bands are very small (low dose, n=3; high dose n=4). Nonetheless the PK steady state trough results (week 16) for the high dose groups (102 to 116µg/mL) are generally in line with those from the adult pivotal studies (98 to 101 µg/mL). As would be expected, steady state trough results from the low dose groups are lower (40 to 78 µg/mL).

Tmax was observed to be 3-4 days in the study, lower than that observed for the adult pivotal studies of 5-8 days. The MAH should monitor and/or discuss this aspect in any future regulatory submissions.

PD results

Staphylococcus Aureus

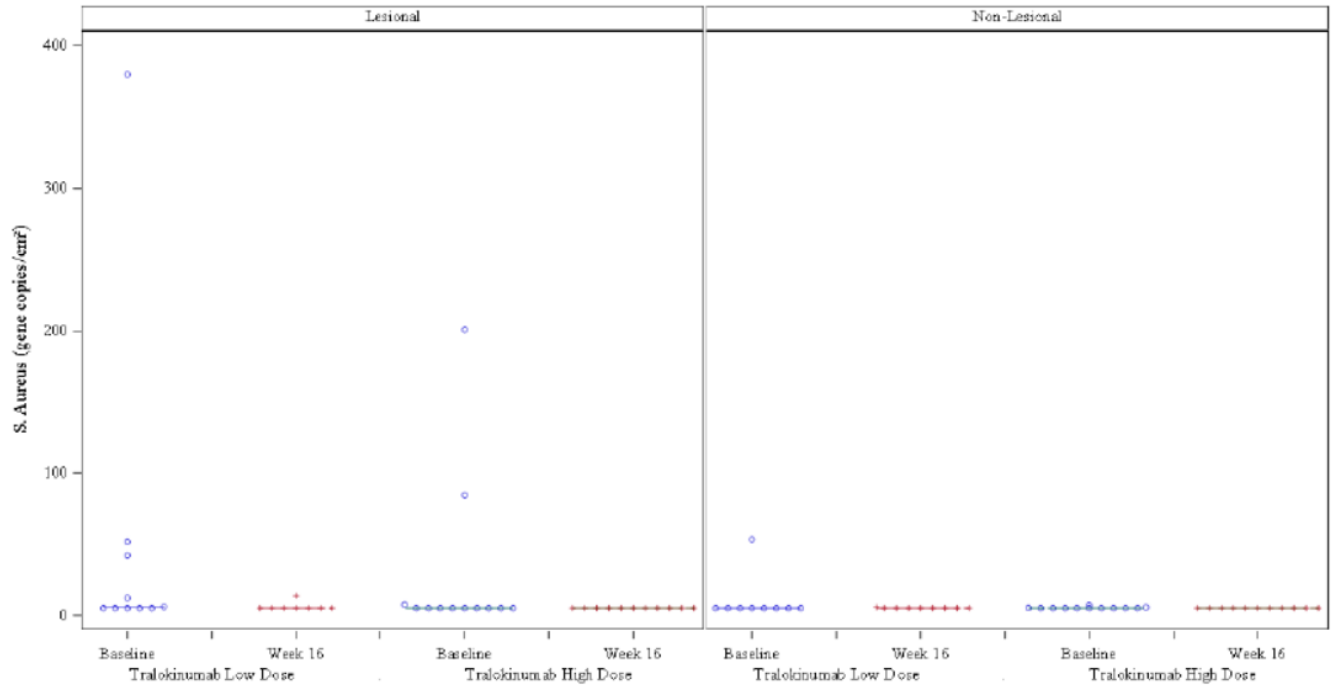
Swab sample analysis

In this trial, LP0162-1335, 23 participants gave consent to collection of skin swabs for S. Aureus analysis, 10 from the low dose group and 13 from the high dose group. Due to the small sample size, the data were analysed according to high or low dose, but not sub-divided further into weight groups.

Baseline characteristics S. Aureus

At baseline/Week 0, most of the samples from lesional skin had S. Aureus copy number levels BLQ, across the 2 dose groups. For the non-lesional samples only one sample was above LLoQ for S. Aureus in each of the 2 dose groups, respectively, Panel 8.

Panel 8 Abundance of *Staphylococcus Aureus* at baseline and after 16 weeks of tralokinumab low or high dose in lesional and non-lesional skin.



Values below LLoQ were set to 4.88 CN/cm^2.

Comparing *S. Aureus* abundance between lesional and non-lesional skin at baseline, a significant difference was seen for the low dose group, but not for the high dose group, Panel 9.

Panel 9 Statistical analysis of *Staphylococcus Aureus* abundance

		Tralokinumab Low Dose (n=10)	Tralokinumab High Dose (n=13)
Lesional vs Non-Lesional in Baseline			
S Aureus (gene copies/cm^2)	N	9	12
	Mean Difference (95% CI)	2.272 (1.013, 5.094)	1.712 (0.788, 3.720)
	P-value	0.0472	0.1554
Week 16 vs Baseline in Lesional			
S Aureus (gene copies/cm^2)	N	8	10
	Mean Difference (95% CI)	0.428 (0.103, 1.775)	0.497 (0.185, 1.338)
	P-value	0.2012	0.1448
Week 16 vs Baseline in Non-Lesional			
S Aureus (gene copies/cm^2)	N	8	10
	Mean Difference (95% CI)	0.742 (0.366, 1.503)	0.948 (0.871, 1.032)
	P-value	0.3506	0.1866

Paired T-Test was performed on log-transformed levels and results were exponentiated back to the original scale. n = the full analysis set. Values <LLOQ were set to 4.88 gene copies/cm^2.

Effect of treatment on *S. Aureus*

The other endpoint in the CTP for skin swab analysis is defined as: Change in number of *S. Aureus* gene-copies per cm2 from Week 0 to Week 16.

For the lesional samples at week 16, only 1 of the 8 samples from the low dose group was above LLoQ and all 11 samples in the high dose group were below LLoQ, Panel 8.

For the non-lesional samples at week 16, 1 of the 9 samples from the low dose group was just above LLoQ with the other 8 being BLQ and all 11 samples from the high dose group were BLQ, Panel 8.

Comparing *S. Aureus* abundance in lesional samples at baseline to week 16, a non-significant decrease in mean number of *S. Aureus* gene-copies per cm2 was seen for both dose groups. For the non-lesional samples, only 1 sample was above LLoQ at baseline in the low and high dose group, respectively, hence, no further interpretation of the data is made, Panel 9.

Sphingomyelin

Skin tape strip analysis

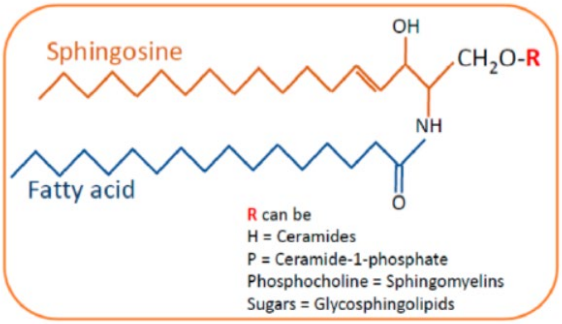
Skin tape stripping is a minimally invasive, nonscarring approach utilizing serial adhesive films to capture the stratum corneum and the upper part of the granular layer to investigate skin barrier integrity and function. Skin tape strips have been used to investigate the level of metabolites and lipids in AD skin.

In this trial, LP0162-1335, 23 participants gave consent to collection of skin tape strips for analysis of skin lipids, 10 from the low dose group and 13 from the high dose group. Tape strip samples were collected at baseline and week 16 from both lesional and non-lesional AD skin.

Due to the small sample size, the data were analysed according to high or low dose, but not sub-divided further into weight groups.

This report includes data on changes in SM. SMs are sphingolipids, as are ceramides and glycosphingolipids. All 3 groups consist of a sphingosine backbone linked to a fatty acid chain that can vary in length. The 3 groups differ by the structure of their head as indicated by an "R" in Panel 10. E.g., SMs have a phosphocholine head.

Panel 10 Structure of sphingolipids



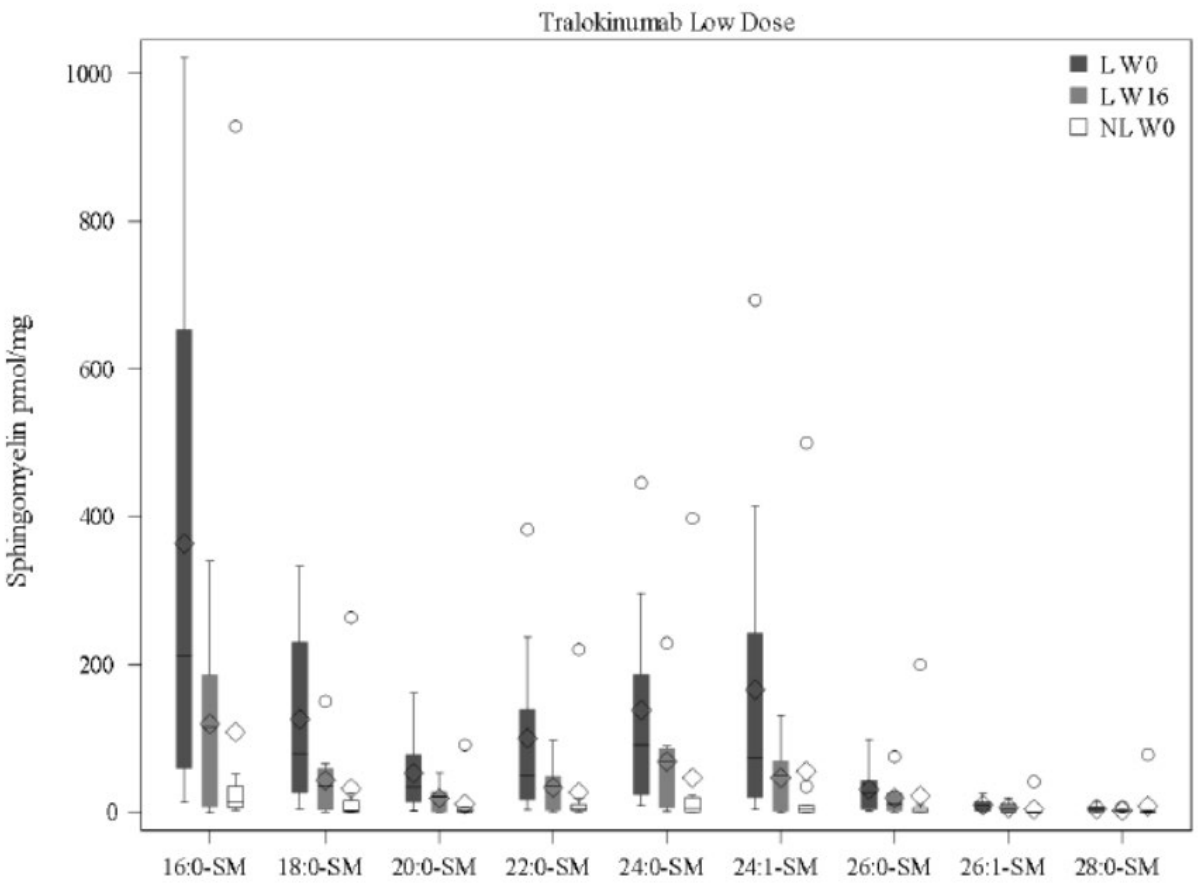
In this report, SMs are abbreviated according to the carbon number and double bonds in their fatty acid chain e.g., 18:1–SM, denotes a SM with a fatty chain of 18 carbon atoms and 1 double bond.

This report includes data for total SM and the individual SMs: 16:0-SM, 18:0-SM, 20:0-SM, 22:0-SM, 24:0-SM, 24:1-SM, 26:0-SM, 26:1-SM, 28:0-SM.

Baseline characteristics sphingomyelin

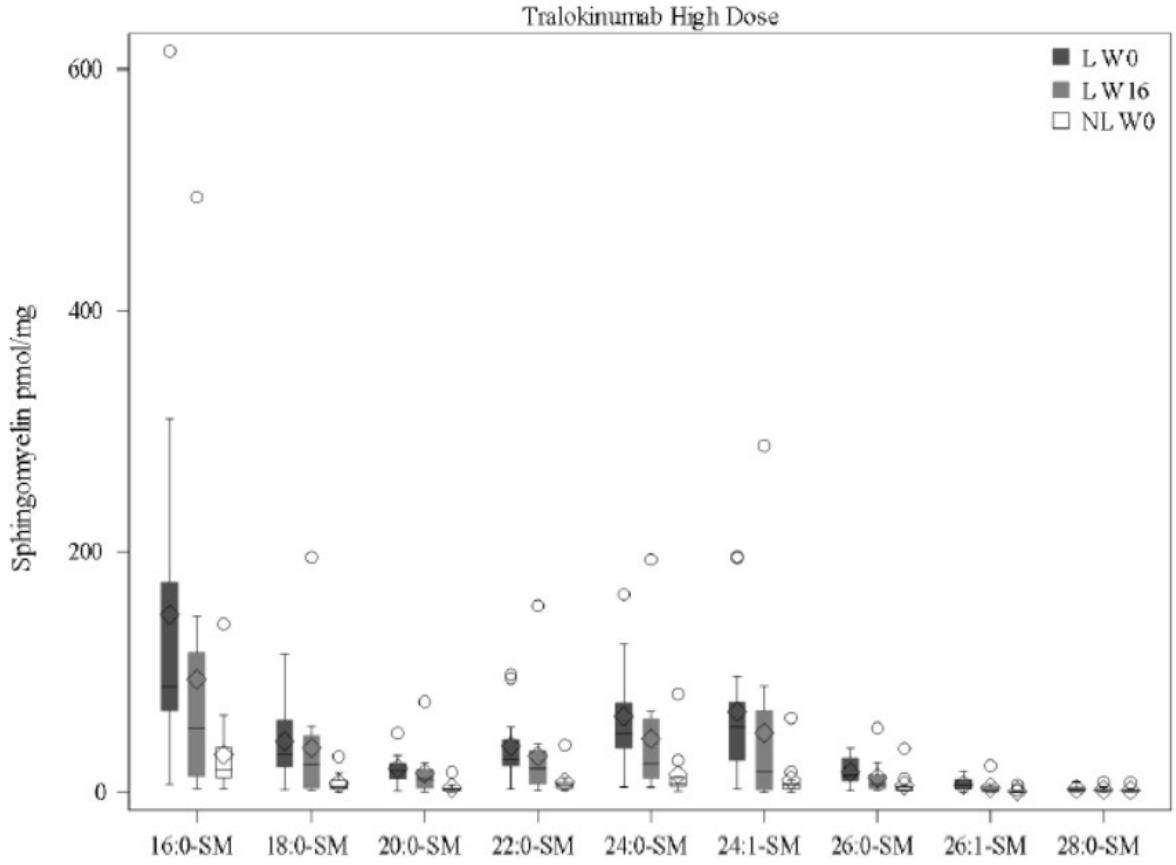
At baseline, levels of both total and individual SMs were low in non-lesional skin with low variability, Panel 11 and Panel 12. For the lesional skin, the levels of most of the SMs was high with high variability except for 26:0-SM, 26:1-SM, and 28:0-SM, that were only detected at low levels. Except for 28:0-SM, all SM groups were significantly higher in lesional compared to non-lesional samples at baseline.

Panel 11 Sphingomyelins at baseline and after 16 weeks of tralokinumab low dose.



In the boxplot, the middle line represents the median; the top and bottom margins of the box represent the 75th and 25th percentiles; the whiskers are calculated as 1.5*Inter Quartile Range. The small open dots outside of whiskers are outliers; the open diamond in the box indicates the group mean value. L = lesional; NL = non-lesional; W0 = baseline/Week 0; W16 = Week 16.

Panel 12 Sphingomyelins at baseline and after 16 weeks of tralokinumab high dose.



In the boxplot, the middle line represents the median; the top and bottom margins of the box represent the 75th and 25th percentiles; the whiskers are calculated as 1.5*Inter Quartile Range. The small open dots outside of whiskers are outliers; the open diamond in the box indicates the group mean value.

Effect of treatment on sphingomyelin

The exploratory endpoint in the CTP for skin tape strips analysis is defined as: Change in amount of SM in skin tape strips from Week 0 to Week 16.

In the lesional samples, a tendency to a decrease in mean amount of SM from baseline to Week 16 was seen in both the low and high tralokinumab dose group, for total and individual SMs, but none of the changes were significant.

In the non-lesional samples, a tendency to a decrease from baseline to Week 16 was seen for the low dose group, with no significant changes. For non-lesional samples in the high dose group, a significant decrease was seen from baseline to Week 16 for total SMs and all individual SMs, except for 20:0-SM and 22:0-SM.

CHMP comment:

The MAH presents PD data on *S. Aureus* (swabs) and sphingomyelin (tapes for lipid analysis) from 23 of 28 patients. For *S. Aureus,* a statistically significant difference between lesional and non-lesional skin at baseline for the low dose group was observed, however there was no statistically significant difference observed for the same in the high dose group, nor when comparing skin at week 16 to baseline. However, the majority of patients had levels below the limit of quantitation at baseline thus calling into question the reliability of any results.

Results for sphingomyelin demonstrated a significant decrease for non-lesional skin in the high dose group at Week 16 compared to baseline, however no significant changes were found for the lesional skin at Week 16 compared to baseline, or in the low dose group.

Efficacy results

All efficacy endpoints were analysed using the FAS. Continuous efficacy endpoints are presented as observed. Binary efficacy endpoints are presented as observed and using a composite estimand strategy. The composite estimand strategy assumed that initiation of rescue treatment and permanent discontinuation of IMP indicated failure of the treatment to achieve response. Thus, subjects who received rescue treatment or permanently discontinued IMP prior to the analysis time point were imputed as non-responders. Additionally, subjects with missing data at the analysis time point were imputed as non-responders. It should be noted that a large proportion of the trial population used rescue medication during the trial with many subjects initiating rescue medication already in the beginning of the initial treatment period. Furthermore, although TCS and TCI were prohibited in the initial treatment period, the trial design allowed use of TCS and TCI prior to and at the time of enrolment in the trial and accordingly some of the enrolled subjects used TCS and TCI already at randomization. Consequently, according to the composite estimand strategy, a substantial proportion of the subjects was defined as non-responders, some of the subjects already at baseline. The composite estimand strategy is therefore considered inappropriate to investigate the treatment effect in the present trial and focus will therefore be on observed data in the following sections.

Improvements in the severity and extent of AD as well as patient-reported outcomes supported the efficacy of tralokinumab in children (age 6 to <12 years) with moderate-to-severe AD over a treatment period of up to 68 weeks (Panel 21 and Panel 22).

Panel 21 Summary of efficacy results – secondary endpoints – full analysis set

Endpoint	Low 150 mg Q4W or 150 mg Q2W 150 mg Q2W (N = 13)	High 150 mg Q2W or 300 mg Q2W 150 mg Q2W (N = 15)	Total 150 mg Q2W (N = 28)
Change in SCORAD from Week 0 to Week 68			
n	11	10	21
Mean (SD)	-39.79 (18.24)	-41.05 (16.66)	-40.39 (17.08)
Change in POEM from Week 0 to Week 68			
n	11	10	21
Mean (SD)	-15.00 (7.31)	-14.20 (9.19)	-14.62 (8.05)
Change in EASI from Week 0 to Week 68			
n	11	10	21
Mean (SD)	-22.46 (6.63)	-25.89 (11.69)	-24.09 (9.30)

Abbreviations: EASI = Eczema Area and Severity Index; N = number of subjects in analysis set; n = number of subjects with observation; POEM = Patient Oriented Eczema Measure; Q2W = every 2 weeks; Q4W = every 4 weeks; SCORAD = Scoring Atopic Dermatitis; SD = standard deviation.

Panel 22 Summary of efficacy results – other endpoints – full analysis set

Endpoint	Low 150 mg Q4W or 150 mg Q2W 150 mg Q2W (N = 13)	High 150 mg Q2W or 300 mg Q2W 150 mg Q2W (N = 15)	Total 150 mg Q2W (N = 28)
EASI-75 at Week 16			
n	13	14	-
Responders (%)[a]	6 (46.2%)	6 (42.9%)	-
IGA 0/1 at Week 16			
n	13	15	-
Responders (%)[a]	3 (23.1%)	1 (6.7%)	-
EASI-75 at Week 68			
n	11	10	21
Responders (%)[a]	9 (81.8%)	9 (90.0%)	18 (85.7%)
IGA 0/1 at Week 68			
n	11	10	21
Responders (%)[a]	6 (54.5%)	2 (20.0%)	8 (38.1%)
Change in SCORAD from Week 0 to Week 16			
n	13	14	-
Mean (SD)	-26.85 (23.37)	-25.02 (18.18)	-
Change in POEM from Week 0 to Week 16			
n	12	14	-
Mean (SD)	-9.67 (4.94)	-10.71 (7.14)	-
Change in EASI from Week 0 to Week 16			
n	13	14	-
Mean (SD)	-13.47 (14.96)	-17.94 (12.36)	-
Rescue medication (yes/no) during the initial treatment period			
n	13	15	28
Yes (%)	7 (53.8%)	11 (73.3%)	18 (64.3%)
Rescue medication (yes/no) during the open-label treatment period			
n	13	15	28
Yes (%)	5 (38.5%)	7 (46.7%)	12 (42.9%)

Notes: a) Observed cases.

Abbreviations: EASI = Eczema Area and Severity Index; EASI-75 = at least 75% reduction in EASI score; IGA = Investigator's Global Assessment; IGA 0/1 = a score of *clear* or *almost clear* on the IGA scale; N = number of subjects in analysis set; n = number of subjects with observation; POEM = Patient Oriented Eczema Measure; Q2W = every 2 weeks; Q4W = every 4 weeks; SCORAD = Scoring Atopic Dermatitis; SD = standard deviation.

CHMP comment:

Efficacy results demonstrated comparable changes from baseline to week 16 and week 68 for the SCORAD, POEM and EASI endpoints across both high and low dose groups. Similarly comparable results were demonstrated across both higher and lower dose groups for EASI75 at week 16 and 68. A lower percentage of patients in the lower dose group needed rescue treatment at both week 16 and 68.

Across both treatment groups, comparable percentages of patients achieved IGA 0/1 at week 16 (primary endpoint) compared to the pivotal adult studies – 23% (lower dose), 7% (higher dose), 16% (ECZTRA 1), 22% (ECZTRA 2)

Across both treatment groups, higher percentages of patients achieved EASI75 at week 16 (primary endpoint) compared to the pivotal adult studies – 46% (lower dose), 49% (higher dose), 25% (ECZTRA 1), 33% (ECZTRA 2)

Overall, these results may be suggestive of comparable efficacy results in paediatrics (6 to <12 years old) compared to adults with moderate to severe AD, although patient numbers are small, and this is not a controlled trial.

Safety results

Initial treatment period

AEs by frequency

A total of 23 subjects reported 93 AEs during the initial treatment period; 10 subjects reported 42 events in the low-dose group and 13 subjects reported 51 AEs in the high-dose group (Panel 18). The percentage of subjects reporting AEs and the rate of AEs was similar between the low-dose group (76.9%, 1051.36 events per 100 PYE) and the high-dose group (86.7%, 1130.48 events per 100 PYE) (Panel 18).

At the PT level, most AEs were reported only once, with no particular reporting pattern or clustering across SOCs and no meaningful differences between treatment groups. The SOCs with the most frequently reported AEs were 'infections and infestations' (reported by 46.2% of subjects in the low-dose group and 60.0% of subjects in the high-dose group) and 'respiratory, thoracic and mediastinal disorders' (reported by 46.2% of subjects in the low-dose group and 20.0% of subjects in the high-dose group).

The most frequently reported AEs (reported by ≥10% of subjects in any treatment group) were PTs (Panel 18):

• Nasopharyngitis reported by 2 subjects (15.4%) in the low-dose group and by 4 subjects (26.7%) in the high-dose group.

• Headache reported by 3 subjects (23.1%) in the low-dose group and by 2 subjects (13.3%) in the high-dose group.

• Oropharyngeal pain reported by 2 subjects (15.4%) in the low-dose group.

• Abdominal pain upper reported by 1 subject (7.7%) in the low-dose group and by 2 subjects (13.3%) in the high-dose group.

• Respiratory tract infection viral reported by 1 subject (7.7%) in the low-dose group and by 2 subjects (13.3%) in the high-dose group.

• Cough reported by 1 subject (7.7%) in the low-dose group and by 2 subjects (13.3%) in the high-dose group.

• Injection site reaction reported by 2 subjects (13.3%) in the high-dose group.

AEs by relation to IMP

The proportion of subjects with AEs assessed as probably or possibly related to the IMP and the rate of related AEs was slightly higher in the high-dose group (60.0%, 642.82 events per 100 PYE) compared to the low-dose group (46.2%, 425.55 events per 100 PYE) (Panel 18).

Of note, the relatively high rate of related AEs was partly driven by a single site having a considerably higher rate of related AEs compared to all other participating. This site contributed with 2 subjects in the low-dose group and 4 subjects in the high-dose group who all reported at least one related AE. The reason for the high rate of related AEs at this site is being investigated at the time of this interim CTR. At the PT level, most related AEs were reported only once, with no particular reporting pattern or clustering across SOCs and no meaningful differences between treatment groups.

The most frequently reported AEs (reported by ≥10% of subjects in any treatment group) were PTs:

• Headache reported by 1 subject (7.7%) in the low-dose group and 2 subjects (13.3%) in the high-dose group.

• Injection site reaction reported by 2 subjects (13.3%) in the high-dose group.

AEs by severity

All AEs were mild or moderate in severity. Moderate AEs were reported in a slightly higher proportion of subjects in the low-dose group (38.5%) compared to the high-dose group (13.3%) (Panel 18). No severe events were reported.

SAEs

In the initial treatment period, 1 SAE of PT 'asthma' was reported in a subject from the low-dose group (Panel 18). The SAE was moderate and assessed as not related to IMP.

AEs of special interest

No AESIs (conjunctivitis, keratoconjunctivitis, and keratitis) were reported in the initial treatment period (Panel 18)

Panel 18 Overview of AEs - initial treatment period - initial safety analysis set

	Low 150 mg Q4W or 150 mg Q2W (N = 13, PYE = 3.99)			High 150 mg Q2W or 300 mg Q2W (N = 15, PYE = 4.51)		
	n (%)	E	R	n (%)	E	R
Overall summary:						
AEs	10 (76.9)	42	1051.36	13 (86.7)	51	1130.48
SAEs	1 (7.7)	1	25.03	0	0	0
Severity:						
Mild	10 (76.9)	30	750.97	12 (80.0)	49	1086.15
Moderate	5 (38.5)	12	300.39	2 (13.3)	2	44.33
Severe	0	0	0	0	0	0
Related to IMP[a]	6 (46.2)	17	425.55	9 (60.0)	29	642.82
AEs leading to withdrawal from the trial or permanent discontinuation of IMP	0	0	0	0	0	0
Outcome:						
Fatal	0	0	0	0	0	0
Not recovered/not resolved	2 (15.4)	2	50.06	2 (13.3)	3	66.50
Recovering/resolving	1 (7.7)	1	25.03	0	0	0
Recovered/resolved	10 (76.9)	39	976.26	13 (86.7)	48	1063.99
Recovered/resolved with sequalae	0	0	0	0	0	0
Most frequently (≥10% of subjects) reported AEs, by PT:						
Nasopharyngitis	2 (15.4)	2	50.6	4 (26.7)	4	88.67
Headache	3 (23.1)	3	75.10	2 (13.3)	3	66.50
Oropharyngeal pain	2 (15.4)	2	50.06	0	0	0
Abdominal pain upper	1 (7.7)	4	100.13	2 (13.3)	2	44.33
Respiratory tract infection viral	1 (7.7)	2	50.06	2 (13.3)	2	44.33
Cough	1 (7.7)	1	25.03	2 (13.3)	2	44.33
Injection site reaction	0	0	0	2 (13.3)	2	44.33
Adverse events of special interest:						
Conjunctivitis	0	0	0	0	0	0
Keratoconjunctivitis	0	0	0	0	0	0
Keratitis	0	0	0	0	0	0

Notes: a) Considered possibly or probably related by the investigator.
Abbreviations: AE = adverse event; E = number of events; IMP = investigational medicinal product; N = number of subjects in analysis set; n = number of subjects with one or more events; PT = preferred term; PYE = patient years of exposure; Q2W = every 2 weeks; Q4W = every 4 weeks; R = rate (number of events divided by patient years of exposure multiplied by 100); SAE = serious adverse event.

Open-label treatment period

AEs by frequency

A total of 25 subjects (96.2%) reported 176 AEs (744.88 events per 100 PYE) during the open-label treatment period with no pronounced difference between subjects treated with the low-dose regimen or the high-dose regimen during the initial treatment period (Panel 19).

At the PT level, most AEs were reported only once or twice, with no particular reporting pattern or clustering across SOCs. The SOCs with the most frequently reported AEs were 'infections and infestations' (reported by 88.5% of the subjects) and 'general disorders and administration site conditions' (reported by 42.3% of the subjects).

The most frequently reported AEs (reported by ≥10% of subjects) were PTs (Panel 19):

- Nasopharyngitis reported by 8 subjects (30.8%).
- Headache reported by 6 subjects (23.1%).
- Gastroenteritis reported by 5 subjects (19.2%).
- Pyrexia reported by 5 subjects (19.2%).
- Upper respiratory tract infection reported by 5 subjects (19.2%).
- Oropharyngeal pain reported by 4 subjects (15.4%).
- Injection site reaction reported by 3 subjects (11.5%).
- Influenza reported by 3 subjects (11.5%).
- Abdominal pain upper reported by 3 subjects (11.5%).
- Gastroenteritis viral reported by 3 subjects (11.5%).
- COVID-19 reported by 3 subjects (11.5%).
- Eosinophil count increased reported by 3 subjects (11.5%).
- Nausea reported by 3 subjects (11.5%).

AEs by relation to IMP

A total of 11 subjects (42.3%) had AEs assessed as probably or possibly related to IMP (347.05 events per 100 PYE) during the open-label treatment period with no pronounced difference between subjects treated with the low-dose regimen or the high-dose regimen during the initial treatment period (Panel 19).

As was the case in the initial treatment period, one particular site contributed with a high proportion of related AEs. At the PT level, most related AEs were reported only once, with no particular reporting pattern or clustering across SOCs. The most frequently reported AEs (reported by ≥10% of subjects) were PTs:

- Headache reported by 4 subjects (15.4%).
- Nasopharyngitis reported by 4 subjects (15.4%).
- Eosinophil count increased reported by 3 subjects (11.5%).
- Injection site reaction reported by 3 subjects (11.5%).

AEs by severity

All but 1 AEs were mild or moderate in severity (Panel 19). 1 severe AE of PT 'dehydration' was reported in a subject who had been treated with the high-dose regimen in the initial treatment period. This severe event of 'dehydration' was also reported as an SAE.

SAEs

In the open-label treatment period, 1 SAE of PT 'dehydration' was reported (Panel 19). The SAE was severe and assessed as not related to IMP.

AEs of special interest

In the open-label treatment period, 2 AESIs of PT 'conjunctivitis' were reported by 2 subjects (Panel 19). Both AESIs were non-serious, mild, and assessed by the investigator as probably or possibly related to the IMP. Both subjects recovered from the events.

Panel 19 Overview of AEs - open-label treatment period - open-label safety analysis set

	Low 150 mg Q4W/150 mg Q2W 150 mg Q2W (N = 12, PYE = 11.22)			High 150 mg Q2W/300 mg Q2W 150 mg Q2W (N = 14, PYE = 12.41)			Total 150 mg Q2W (N = 26, PYE = 23.63)		
	n (%)	E	R	n (%)	E	R	n (%)	E	R
Overall summary:									
AEs	11 (91.7)	79	704.31	14 (100.0)	97	781.55	25 (96.2)	176	744.88
SAEs	0	0	0	1 (7.1)	1	8.06	1 (3.8)	1	4.23
Severity:									
Mild	10 (83.3)	74	659.73	14 (100.0)	87	700.98	24 (92.3)	161	681.40
Moderate	3 (25.0)	5	44.58	5 (35.7)	9	72.51	8 (30.8)	14	59.25
Severe	0	0	0	1 (7.1)	1	8.06	1 (3.8)	1	4.23
Related to IMP[a]	5 (41.7)	35	312.04	6 (42.9)	47	378.69	11 (42.3)	82	347.05
AEs leading to withdrawal from the trial or permanent discontinuation of IMP	0	0	0	0	0	0	0	0	0
Outcome:									
Fatal	0	0	0	0	0	0	0	0	0
Not recovered/not resolved	1 (8.3)	2	17.83	3 (21.4)	5	40.29	4 (15.4)	7	29.63
Recovering/resolving	1 (8.3)	1	8.92	1 (7.1)	1	8.06	2 (7.7)	2	8.46
Recovered/resolved	11 (91.7)	74	659.73	14 (100.0)	91	733.21	25 (96.2)	165	698.33

Recovered/resolved with sequalae	1 (8.3)	1	8.92	0	0	0	1 (3.8)	1	4.23
Missing	1 (8.3)	1	8.92	0	0	0	1 (3.8)	1	4.23
Most frequently (≥10% of subjects) reported AEs, by PT:									
Nasopharyngitis	3 (25.0)	6	53.49	5 (35.7)	12	96.69	8 (30.8)	18	76.18
Headache	2 (16.7)	2	17.83	4 (28.6)	5	40.29	6 (23.1)	7	29.63
Gastroenteritis	2 (16.7)	3	26.75	3 (21.4)	5	40.29	5 (19.2)	8	33.86
Pyrexia	2 (16.7)	2	17.83	3 (21.4)	5	40.29	5 (19.2)	7	29.63
Upper respiratory tract infection	1 (8.3)	1	8.92	4 (28.6)	6	48.34	5 (19.2)	7	29.63
Oropharyngeal pain	3 (25.0)	5	44.58	1 (7.1)	1	8.06	4 (15.4)	6	25.39
Injection site reaction	2 (16.7)	2	17.83	1 (7.1)	6	48.34	3 (11.5)	8	33.86
Influenza	0	0	0	3 (21.4)	7	56.40	3 (11.5)	7	29.63
Abdominal pain upper	1 (8.3)	1	8.92	2 (14.3)	3	24.17	3 (11.5)	4	16.93
Gastroenteritis viral	1 (8.3)	2	17.83	2 (14.3)	2	16.11	3 (11.5)	4	16.93
COVID-19	3 (25.0)	3	26.75	0	0	0	3 (11.5)	3	12.70
Eosinophil count increased	1 (8.3)	1	8.92	2 (14.3)	2	16.11	3 (11.5)	3	12.70
Nausea	3 (25.0)	3	26.75	0	0	0	3 (11.5)	3	12.70
Adverse events of special interest:									
Conjunctivitis	1 (8.3)	1	8.92	1 (7.1)	1	8.06	2 (7.7)	2	8.46
Keratoconjunctivitis	0	0	0	0	0	0	0	0	0
Keratitis	0	0	0	0	0	0	0	0	0

Notes: a) Considered possibly or probably related by the investigator.
Abbreviations: AE = adverse event; E = number of events; IMP = investigational medicinal product; N = number of subjects in analysis set; n = number of subjects with one or more events; PT = preferred term; PYE = patient years of exposure; R = rate (number of events divided by patient years of exposure multiplied by 100); SAE = serious adverse event.

Others

There were no deaths in the trial (Panel 18, Panel 19). There were no AEs leading to withdrawal from trial or permanent discontinuation of IMP (Panel 18, Panel 19). There were no pregnancies reported in the trial. No trial-related product complaints were reported.

Clinical laboratory evaluation

Biochemistry, hematology, and serology

Mean values of most biochemistry and hematology parameters showed only minor fluctuations within the normal reference ranges throughout the trial.

For alkaline phosphatase, a minor increase in mean values within the normal range was observed from baseline to the end of the open-label period in both treatment groups. Furthermore, a few shifts from normal to high alkaline phosphatase values were observed and 1 AE related to increases in alkaline phosphatase was reported. As only total alkaline phosphatase was assessed, changes in tissue specific alkaline phosphatase isoenzymes (including liver alkalic phosphatase isoenzyme) is unavailable. However, no clinically relevant changes were observed for other liver parameters.

For eosinophils, mean values were above the upper limit of the normal reference range at baseline in both treatment groups as expected in subjects with AD. The mean eosinophil values transiently

increased in the beginning of the initial treatment period in both treatment groups and subsequently decreased to baseline values by the end of the open-label treatment period. A few shifts from normal to high eosinophils values were observed. Furthermore, a few AEs related to eosinophils were reported. Of note, eosinophilia is a known ADR according to the product information for tralokinumab.

IgE was included as a serum biomarker. As expected in subjects with AD, the mean IgE values were above the normal reference range at baseline (low-dose group: mean IgE = 2004.1 IU/mL; high-dose group: mean IgE = 3740.7 IU/mL), decreased over time, but remained above the normal reference range during the entire treatment period. 1 event of blood immunoglobin E increased was reported during the trial.

The findings and observations related to laboratory parameters were generally comparable across treatment groups and did not give rise to any safety concerns.

Laboratory abnormalities reported as adverse events

A laboratory abnormality was reported as an AE if the abnormality was considered clinically significant by the investigator. Few AEs related to clinical laboratory parameters were identified within the SOCs 'investigations' and 'blood and lymphatic system disorders' as described below for each treatment period.

Initial treatment period

Within the SOC 'investigations', 1 event of PT 'blood alkaline phosphatase' was reported for a subject in the low-dose group. The event was mild, non-serious, assessed as not related to IMP, and was recovered/resolved.

Open-label treatment period

Within the SOC 'blood and lymphatic systems', the following events were reported:

• 2 events of PT 'eosinophilia' were reported for 2 subjects. 1 of the events was mild, non-serious, assessed as probably related to IMP, and was not recovered/not resolved. The other event was moderate, non-serious, assessed as possibly related to IMP, and was recovered/resolved.

• 1 event of PT 'neutropenia' was reported. The event was mild, non-serious, assessed as not related to IMP and was recovered/resolved. Within the SOC 'investigations', the following events were reported:

• 3 events of PT 'eosinophil count increased' reported for 3 subjects. All events were non-serious, mild or moderate, and assessed as possibly related to IMP. One of the event was recovered/resolved, whereas the other 2 were recovering/resolving or not recovered/resolved.

• 1 event of PT 'blood immunoglobin E increased'. The event was moderate, non-serious, assessed as possibly related to IMP, and was recovered/resolved.

Antibodies

Antibodies to tralokinumab in serum were measured by a validated bioanalytical method as described in the bioanalytical report (Determination of Tralokinumab, Anti-Tralokinumab Antibodies and Neutralizing Anti-Tralokinumab Antibodies in Human Serum Samples from Clinical Study LP0162-1335).

None of the subjects developed ADA during the trial.

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

Vital signs

No clinically relevant changes in vital signs measurements (systolic and diastolic blood pressure, pulse rate, and body temperature) were observed from baseline to Week 68. The findings were similar across treatment groups. 1 AE related to vital signs was identified within the SOC 'vascular disorders' (PT: 'essential hypertension'). The event was reported in the initial treatment period for a subject in the low-dose group and was initially assessed as mild, but later developed to moderate severity. The event was non-serious, assessed as not related to the IMP, and was recovering/resolving.

Physical examination

Clinically significant abnormal findings at the screening visit were to be documented as medical history. At subsequent visits, any new clinically significant abnormal finding in physical examination, or a deterioration of a pre-existing condition, were to be reported as an AE.

2 clinically significant abnormal findings in physical examination were observed for 2 subjects during the trial:

• 1 subject had an abnormal finding of 'obesity' at screening

• 1 subject in the low-dose group had an abnormal finding of 'scarlet fever' in the initial treatment period (Week 8).

Electrocardiogram

No clinically relevant changes in ECG parameters were observed from baseline to Week 68. No differences between the treatment groups were observed.

CHMP comment:

Safety results from the initial treatment phase demonstrated a slightly lower number of AEs in the lower dose group compared to the higher dose group (77% v 87%). All AEs were mild or moderate. The rate of related AEs was 46% and 60% in the lower and higher dose groups. The only related AE which occurred in more than 2 subjects, was headache. Headache is not listed as an ADR in the SmPC.

There was 1 SAE, asthma, not considered to be related to the IMP, the patient had a history of asthma. There were no severe AEs or AESI.

Safety results from the open label treatment phase demonstrated a slightly lower number of AEs in the lower dose group compared to the higher dose group (92% v 100%). Most AEs were mild or moderate. The rate of related AEs was 42 and 43% in % in the lower and higher dose groups. The related AEs which occurred in more than 2 subjects were injection site reaction, nasopharyngitis, headache, and eosinophil count increased. Injection site reaction and eosinophil count increased (eosinophilia) are already listed as ADRs in the SmPC. Nasopharyngitis could be considered as falling under the ADR upper respiratory tract infection. Therefore again, headache is the only related AE reported from this trial that is not listed in the SmPC as an ADR. Overall, however, considering the small sample size of this trial and the low numbers of patients reporting headache, together with headache being a mild, easily treatable and commonly occurring AE in the general population, it is agreed updates to the SmPC are not currently warranted, however the MAH should continue to monitor this AE.

The MAH suggests a single investigator site which recruited 6 patients contributed to the high rate of related AEs reported, the reason for this high rate of related AEs is currently being investigated, the MAH should discuss their findings in any relevant future regulatory submissions.

There was 1 SAE in the open label phase of the trial, dehydration, which was not considered to be related to the IMP. This SAE was also considered severe. It was the only severe AE reported in the trial. There were 2 AESI, conjunctivitis, reported in the open label phase of the trial, conjunctivitis is a known ADR of tralokinumab and is listed in sections 4.4 and 4.8 of the SmPC.

Throughout the study, there were no deaths, no pregnancies, no AEs leading to withdrawal from the trial or permanent discontinuation of IMP and no ADA positive subjects. There were no clinically relevant changes in ECG parameters or vital signs throughout the trial. Only a small number of clinical

laboratory evaluations were reported as AEs, most of these were related to eosinophilia as discussed above.

Overall, these results in paediatrics patients (6 to <12 years old) with moderate to severe AD can be accepted, although patient numbers are small, and this is not a controlled trial.

2.3.3. Discussion on clinical aspects

This is a small phase 2 trial that is part of a paediatric development plan for tralokinumab. The purpose of this trial is to help determine the optimised dose for the subsequent phase 3 pivotal paediatric trial. As such, two different dosing regimens have been employed in this study based on body weight for the first 16 weeks of the study. The high dose given to patients ≥40kg represents the currently approved adult dose. While this is an open label study, the assessor is blinded which is supported in order to reduce bias.

Inclusion criteria were similar to those for the pivotal trials in adults, with moderate-to-severe atopic dermatitis defined by Investigator's Global Assessment (IGA) score of ≥3, an Eczema Area and Severity Index (EASI) score of ≥ 16 at baseline, and a minimum body surface area (BSA) involvement of ≥ 10% and a previous inadequate response to topical medicinal products (corticosteroids).

An interim report has been submitted which contains complete PK and efficacy data. The final CSR with final safety data will likely be reviewed in greater detail as part of any future extension of indication variation together with the phase 3 paediatric data.

28 patients were randomised and included in the main analysis sets. Patients were an average of 8.7 years old, mainly female and white. Patients on average had baseline disease characteristics of an EASI score of 26.99, SCORAD score of 61.48 and a POEM score of 21.21.

Treatment compliance was high, particularly in the initial treatment phase (>96%).

PK data has been provided which is of limited use due to the different treatment regimes and sampling durations (q2w v q4w) and different doses (150mg v 300mg) involved. In addition, the sample sizes, particularly in the high weight (≥40 kg) bands are very small (low dose, n=3; high dose n=4). Nonetheless the PK steady state trough results (week 16) for the high dose groups (102 to 116µg/mL) are generally in line with those from the adult pivotal studies (98 to 101 µg/mL). As would be expected, steady state trough results from the low dose groups are lower (40 to 78 µg/mL).

Tmax was observed to be 3-4 days in the study, lower than that observed for the adult pivotal studies of 5-8 days. The MAH should monitor and/or discuss this aspect in any future regulatory submissions.

The MAH presents PD data on *S. Aureus* (swabs) and sphingomyelin (tapes for lipid analysis) from 23 of 28 patients. For *S. Aureus,* a statistically significant difference between lesional and non-lesional skin at baseline for the low dose group was observed, however there was no statistically significant difference observed for the same in the high dose group, nor when comparing skin at week 16 to baseline. However the majority of patients had levels below the limit of quantitation at baseline thus calling into question the reliability of any results.

Results for sphingomyelin demonstrated a significant decrease for non-lesional skin in the high dose group at Week 16 compared to baseline, however no significant changes were found for the lesional skin at Week 16 compared to baseline, or in the low dose group.

Efficacy results demonstrated comparable changes from baseline to week 16 and week 68 for the SCORAD, POEM and EASI endpoints across both high and low dose groups. Similarly comparable results were demonstrated across both higher and lower dose groups for EASI75 at week 16 and 68. A

lower percentage of patients in the lower dose group needed rescue treatment at both week 16 and 68.

Across both treatment groups, comparable percentages of patients achieved IGA 0/1 at week 16 (primary endpoint) compared to the pivotal adult studies – 23% (lower dose), 7% (higher dose), 16% (ECZTRA 1), 22% (ECZTRA 2)

Across both treatment groups, higher percentages of patients achieved EASI75 at week 16 (primary endpoint) compared to the pivotal adult studies – 46% (lower dose), 49% (higher dose), 25% (ECZTRA 1), 33% (ECZTRA 2)

Overall, these results may be suggestive of comparable efficacy results in paediatrics (6 to <12 years old) compared to adults with moderate to severe AD, although patient numbers are small and this is not a controlled trial.

Safety results from the initial treatment phase demonstrated a slightly lower number of AEs in the lower dose group compared to the higher dose group (77% v 87%). All AEs were mild or moderate. The rate of related AEs was 46% and 60% in the lower and higher dose groups. The only related AE which occurred in more than 2 subjects was headache. Headache is not listed as ADR in the SmPC.

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Throughout the study, there were no deaths, no pregnancies, no AEs leading to withdrawal from the trial or permanent discontinuation of IMP and no ADA positive subjects. There were no clinically relevant changes in ECG parameters or vital signs throughout the trial. Only a small number of clinical laboratory evaluations were reported as AEs, most of these were related to eosinophilia as discussed above.

Overall, these results in paediatrics patients (6 to <12 years old) with moderate to severe AD can be accepted, although patient numbers are small, and this is not a controlled trial.

3. CHMP overall conclusion and recommendation

Overall, there are no specific issues identified which would warrant an update to the product information at this time, however the submitted report is an interim report for a small, uncontrolled trial in a population the product is not indicated for.

☒ **Fulfilled:**

No further action required, however further data are expected in the context of an extension of indication variation prior to any conclusion on product information amendments is made.

☐ **Not fulfilled:**