Cover Page

Study title:	A 32-week Trial to Evaluate the Efficacy and Safety of Tralokinumab in Subjects With Moderate-to-severe Atopic Hand Eczema Who Are Candidates for Systemic Therapy
LEO Pharma number:	LP0162-2328
NCT number:	NCT05958407
Date:	26-May-2025

Statistical analysis plan

LP0162-2328

A phase 3b, interventional, adaptive, clinical trial to evaluate the efficacy and safety of tralokinumab 300 mg every second week monotherapy compared with placebo in subjects with moderate-to-severe atopic hand eczema who are candidates for systemic therapy (ADHAND)

Design of trial:

Phase 3b – Efficacy and Safety trial

A randomized, blinded, parallel-group, multi-site, adaptive, clinical trial

LEO Pharma	**Trial ID:**	**LP0162-2328**
	Date:	**26-May-2025**
	Version:	**2.0**

Statistical analysis plan statement

Approval statement, LEO Pharma

Electronic signatures made within LEO Pharma Clinical Vault are legally binding equivalent of traditional handwritten signatures. The following persons have approved this statistical analysis plan by using electronic signatures as presented on the last page of this document:

PPD

Biostatistics PPD

PPD

Medical PPD

PPD

QC PPD

Guidance documents

This statistical analysis plan is designed to comply with the standards issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 Structure and Content of Clinical Study Reports, E6 Good Clinical Practice, E9 Statistical Principles for Clinical Trials, and E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials.

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List of panels

List of abbreviations

ADaM	Analysis Data Model
ADRG	Analysis data reviewer's guide
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BILI	Bilirubin
CTP	Clinical trial protocol
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
eCRF	Electronic case report form
eDiary	Electronic diary
FAS	full analysis set
FCS	Full-conditional specifications
GCP	Good Clinical Practice
HECSI	Hand Eczema Severity Index
HECSI-50	At least 50% reduction in EASI score from baseline
HECSI-75	At least 75% reduction in EASI score from baseline
HECSI-90	At least 90% reduction in EASI score from baseline
HEIS	Hand Eczema Impact Scale
HESD	The Hand Eczema Symptom Diary
ICE	Intercurrent event
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator's Global Assessment
IGA-AHE	Investigator's Global Assessment scale for atopic hand eczema
IMP	investigational medicinal product (both placebo and the trial's target product)
LOCF	Last observation carried forward
LSW16	Last subject - week 16

MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measurements
MNAR	Missing not at random
NRI	Non-responder Imputation
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
PT	Preferred term
SAE	Serious adverse event
SAF	Safety analysis set
SD	Standard deviation
SOC	System organ class
STDM	Study Data Tabulation Model
WPAI+CIQ	Work Productivity and Activity Impairment + Classroom Impairment Questionnaire
SHP	Specific Health Problem

Version history

This statistical analysis plan (SAP) for trial LP0162-2328 is based on the clinical trial protocol (CTP) Version 6, dated 13-Nov-2024.

SAP version	Date	Change	Rationale
1.0	22-May-2025	Not applicable	Original version

1 Introduction

The statistical analysis will be performed as outlined in the CTP version 6, dated 13-Nov-2024. This SAP, prepared before the unblinding of the trial (which is planned after the completion of the double-blind treatment period for interim analysis 2) , supplements the CTP and contains a more technical and detailed elaboration of topics related to the specification and implementation of the statistical analysis described in the CTP. The level of detail should enable the reader to reproduce all statistical analyses described in the SAP and the CTP.

Changes to the protocol-planned analyses are described in Section 6, and some supplementary analysis specifications are included in the relevant individual sections.

Data handling decisions and derivation rules used in the analysis datasets are specified in the analysis data reviewer's guide (ADRG) and Data Definition document (define.xml).

Analyses will be performed in 3 phases as listed below:

- **Interim analysis 1 for sample size re-evaluation**: to analyse only the primary endpoint with the purpose of sample size re-evaluation (This interim analysis has already been completed. See Section 5.12.1 for details).
- **Interim analysis 2 at the end of the double-blind period**: to analyse all relevant endpoints to the double-blind period (See Section 5.12.2 for details).
- **Final analyses**: to analyse all remaining endpoints of the trial at the end of the safety follow-up period.

1.1 Trial objectives, estimands, and endpoints

Panel 1: Objectives and Endpoints

Objectives	Endpoints
Primary objective	
To evaluate the efficacy of tralokinumab on severity and extent of **atopic hand eczema (AHE)** compared with placebo in treatment of subjects with moderate-to-severe atopic hand eczema	**Primary endpoint** • **IGA-AHE** score of 0 (clear) or 1 (almost clear) at Week 16. **Key secondary endpoints** • Having a decrease in HECSI of at least 75% (**HECSI-75**) from baseline to Week 16. • Having a decrease in HECSI of at least 50% (**HECSI-50**) from baseline to Week 16. • Having a decrease in HECSI of at least 90% (**HECSI-90**) from baseline to Week 16. • Percentage change in HECSI score from baseline to Week 16. **Secondary endpoints** • Having a ≥2-point reduction in **IGA-AHE** score from baseline to Week 16.
Secondary objective	
To evaluate the efficacy of tralokinumab on severity, extent, itch, pain, sleep, and health-related quality of life compared with placebo in treatment of subjects with moderate-to-severe **atopic hand eczema (AHE)**	**Key secondary endpoints** • Reduction in **HESD itch** score (weekly average) of ≥4 points from baseline to Week 16. • Reduction in **HESD pain** score (weekly average) of ≥4 points from baseline to Week 16 [(a)]. • Percentage change in **HEIS** score from baseline to Week 16. • Percentage change in **DLQI** score from baseline to Week 16. **Secondary endpoints** • Percentage change in **HESD itch** score (weekly average) from baseline to Week 16. • Percentage change in **HESD pain** score (weekly average) from baseline to Week 16. • Change in **WPAI+CIQ:AHE** domain scores from baseline to Week 16. **Other/exploratory endpoints** • Reduction in **HESD itch** score (weekly average) of ≥3 points from baseline to Week 16. • Reduction in **HESD pain** score (weekly average) of ≥3 points from baseline to Week 16 [(b)]. • Percentage change in **HEIS sleep** score (weekly average) from baseline to Week 16.

Objectives	Endpoints
	• Reduction in **DLQI** score of ≥4 points from baseline to Week 16 [(c)].
To evaluate the safety and tolerability of tralokinumab in subjects with moderate-to-severe atopic hand eczema	**Secondary endpoint** • Number of treatment-emergent [(d)] adverse events from baseline to Week 16.
Other objectives	
To evaluate the efficacy of tralokinumab on severity and extent of **AD** compared with placebo in subjects with moderate-to-severe atopic hand eczema	**Other/exploratory endpoints** • Percentage change in **EASI** score from baseline to Week 16. • Change in **EASI** score from baseline to Week 16.
To evaluate the efficacy on severity, extent, itch, pain, sleep, and health-related quality of life and the safety and tolerability of continued tralokinumab treatment in subjects with moderate-to-severe **atopic hand eczema (AHE)** in the open-label treatment period (up to 32 weeks)	**Secondary endpoints** • **IGA-AHE** score of 0 (clear) or 1 (almost clear) at Week 32. • Having a decrease in HECSI of at least 75% (**HECSI-75**) from baseline to at Week 32. • Reduction in **HESD itch** score (weekly average) of ≥4 points from baseline to Week 32. • Reduction in **HESD pain** score (weekly average) of ≥4 points from baseline to Week 32[(a)]. • Percentage change in **HEIS** score from baseline to Week 32. • Percentage change in **DLQI** score from baseline to Week 32. • Change in **WPAI+CIQ:AHE** domain scores from baseline to Week 32. • Number of treatment-emergent [(d)] adverse events during the open-label treatment period (Week 16 to Week 32).

Abbreviations: AD = Atopic dermatitis; AE = adverse event; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; HECSI = Hand Eczema Severity Index; HEIS = Hand Eczema Impact Scale; HESD = Hand Eczema Symptom Diary; IGA-AHE = IGA for Atopic Hand Eczema; WPAI+CIQ:AHE = Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire in atopic hand eczema.

a. Among subjects with a baseline HESD pain score (weekly average) ≥4 points.
b. Among subjects with a baseline HESD pain score (weekly average) ≥3 points.
c. Among subjects with a baseline DLQI score ≥4 points.
d. An event will be considered treatment-emergent if started after the first administration of IMP or, if started before the first administration of IMP and worsened in severity after first dose of IMP.

1.2 Trial design

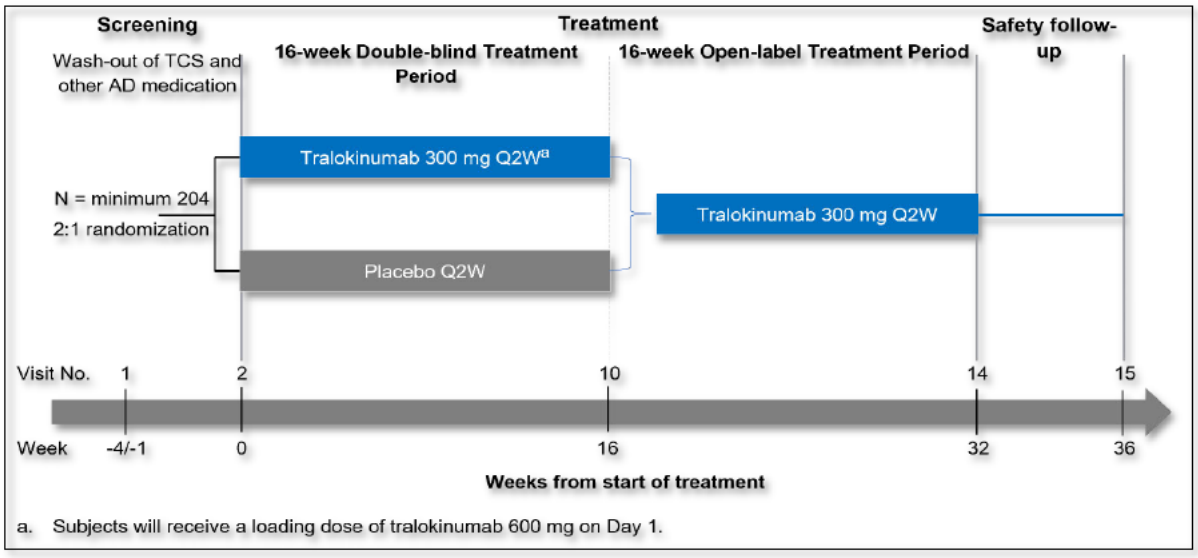
This is a phase 3b, interventional, international, multi-center, randomized, 16-week, double-blind, placebo-controlled, parallel-group, adaptive clinical trial with a 16-week, open-label treatment period. The trial is designed to evaluate the efficacy and safety of 300 mg tralokinumab Q2W compared to placebo in subjects with moderate-to-severe atopic hand eczema. The primary endpoint is assessed at Week 16, and the final efficacy assessments will be conducted at Week 32.

The trial design is illustrated in Panel 2. For each subject (if no discontinuation), the trial is designed to last at least 37 weeks and up to 40 weeks, including:

- a 1-to 4-week screening period
- a 16-week double-blind treatment period (sometimes, referred to as the "Initial period".)
- a 16-week open-label treatment period
- a 4-week safety follow-up period.

The trial design includes a sample size re-evaluation, see Sections 5.6.1 and 5.12.1.

Panel 2 Trial design



Abbreviations: AD = atopic dermatitis; N = number of subjects; Q2W = every 2 weeks; TCS = topical corticosteroids.

2 Testing strategy

2.1 Statistical hypotheses

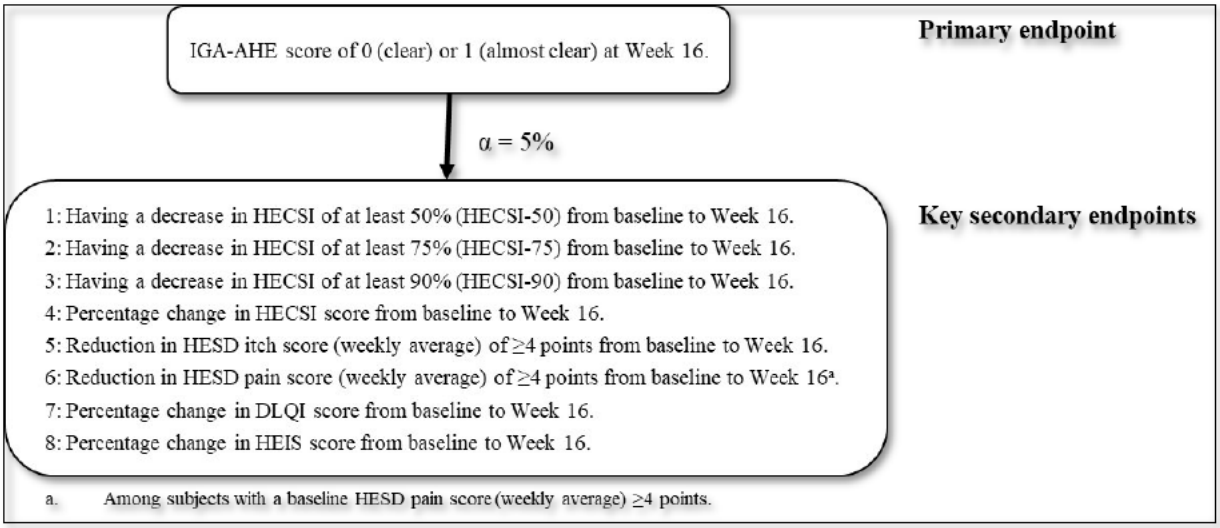
The objective of the primary endpoint is to demonstrate that tralokinumab is superior to placebo in achieving a higher response rate of IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 16. The alternate hypothesis of a positive attributable treatment effect of tralokinumab over placebo will be tested using a 1-sided test at the 2.5% level against the null hypothesis of no attributable effect of tralokinumab compared to placebo.

If the primary endpoint demonstrates that tralokinumab is superior to placebo in achieving a higher response rate of IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 16, then a 5% level will be passed to the key secondary endpoints where superiority of tralokinumab over placebo will be tested using 2-sided tests. 2-sided hypothesis tests can only show superiority when the point estimate of the attributable treatment effect shows that tralokinumab provides an improvement on the applicable endpoint scale over placebo and a p-value lower than the specified alpha level.

2.2 Multiplicity adjustment

The primary and key secondary endpoints will be tested in a hierarchical order using the specified primary estimand analysis. Only if the primary efficacy endpoint leads to a statistically significant result at the one-sided 2.5% level, will the key secondary endpoints be adjusted for multiplicity and tested in the sequential order specified in Panel 3. If one of the endpoints in the testing procedure does not show superiority, then statistical significance in relation to multiplicity will not be declared for any of the subsequent key secondary endpoints, regardless of their p-values.

Panel 3 Multiple testing procedure for the primary and key secondary endpoints



3 Sample size

Sample size documentation is provided in the CTP Section 9.5. The sample size was re-evaluated at interim analysis 1, dated 29-Oct-2024, as described in Section 5.12.1 in the SAP, after 198 subjects were randomized, with 149 evaluable subjects. The minimum number of subjects needed to achieve 90% conditional power was calculated to be 229.

4 Trial analysis sets

All screened subjects will be accounted for in the CTR. For the purposes of analysis, the analysis sets in Panel 4 are defined. Exclusions from the FAS can be considered in special cases as described in ICH E9, Section 5.2.1., Full analysis set. The decisions regarding inclusion/exclusion of subjects or subject data in the trial analysis sets will be documented before breaking the randomization code for interim analysis 2 at the end of the double-blind period and, if needed, for the final analysis at the end of the safety follow-up period.

Panel 4 Trial analysis sets

Trial analysis set	Description	TFL Output based on
Screened	All subjects with informed consent signed (no matter if passed the screening successfully or not).	Disposition/flowchart
Randomized	All enrolled subjects who are randomized. (Enrolled subjects are those who have successfully passed the screening.)	All baseline outputs, compliance, exposure outputs
Full analysis set (FAS)	All randomized subjects who are exposed to at least one dose of IMP. (Subjects will be analysed according to the planned treatment).	All efficacy outputs
Safety analysis set (SAF)	All subjects who are exposed to at least one dose of IMP. (Subjects will be analysed according to the treatment they received).	General safety outputs during the entire treatment periods (e.g. summary of exposure, protocol deviations).
Safety analysis set – Double-blind period (SAF01)	All subjects who are exposed to at least one dose of IMP during the double-blind period. (Subjects will be analyses according to the treatment they received).	Safety outputs corresponding to the double-blind treatment period.
Safety analysis set – Open-label period (SAF02)	All subjects who are exposed to at least one dose of IMP during the open-label period. (Subjects will be analysed according to the treatment they received).	Safety outputs corresponding to the open-label treatment period.
Safety follow-up set (SAFFU)	All subjects who have any data record after the date of the end of the last treatment period.	All safety follow-up outputs

Abbreviations: FAS = full analysis set, IMP = investigational medicinal product, SAF = safety analysis set.

5 Statistical analysis

5.1 General principles

All efficacy analyses will be based on the FAS and all safety analyses will be based on the corresponding SAF as defined in Panel 4.

Baseline measurements are defined as the latest available observation at or prior to the date of the first IMP administration, unless otherwise specified.

The significance test for the primary endpoint will be one-sided using the 2.5% significance level; all other will be two-sided using the 5% significance level. All confidence intervals will be two-sided and presented at the 95% confidence level, unless otherwise specified.

An observed-cases approach will be used for tabulations of data by visit (i.e., involving only those subjects who attended each specific visit).

Observed cases for the double-blind period (Week 0 to Week 16), the open-label treatment period (Week 16 to Week 32), and the safety follow-up period (Week 32 to Week 36) will be reported separately in tables.

Categorical data will be summarized using the number and percentage of subjects in each category and treatment group. Continuous data will be summarized by treatment group using the mean, SD, median, 1st quartile, 3rd quartile, minimum, and maximum values.

For the double-blind period, in addition to “as-observed” tables and figures with descriptive statistics, efficacy data for the double-blind treatment period will be analysed using the estimands defined in Section 5.6 and presented in tables and figures (mean plots) by visit. In all estimand analyses, covariates may be excluded after unblinding if the full model does not converge.

Efficacy data for the open-label period will be presented by visit in tables only “as observed”, i.e. only summaries with descriptive statistics, and no estimand analyses will be performed.

For the entire treatment period, figures (mean plots) of the efficacy data will be presented only for data “as-observed”, where double-blind and open-label periods are combined in one figure per parameter.

Sub-scales (itch and pain) for PGI-S and PGI-C will be tabulated for the double-blind period.

Laboratory measurements only collected at screening will only be listed. Figures for observed cases of the post-baseline laboratory data will be presented for the entire treatment period, i.e., double-blind and open-label periods combined in one figure per parameter.

Subscales which are collected but not defined in an endpoint in Section 3 of the Protocol (e.g. all other HEIS subscales than sleep) will be only presented as a listing. If the total score is not created in the SDTM, it will be derived in ADaM and presented in listings.

5.2 Missing values imputation strategy

Procedures for handling of missing values are included in Sections 5.5 and 5.6 describing the estimand analyses. Missing baseline values will not be imputed.

5.3 Trial periods and date of permanent discontinuation of IMP

The double-blind treatment period starts at visit 2 (week 0) and the open-label treatment period starts at visit 10 (week 16). Definitions of the date of permanent discontinuation of IMP, the start and end of exposure and each trial period are given in Panel 5.

The entire treatment period will be defined as the time from the start of the exposure to the end of the last treatment period (the end of the open-label period, if the subject is not discontinued). Time after the end of the entire treatment period will be defined as the safety follow-up period (SFU) with the start and end dates defined in Panel 5. For subjects with premature permanent discontinuation, the 4-week safety follow-up period starts 2 weeks after the last IMP injection. End of treatment (ET) assessments are considered to take place in the period in which the subject has terminated, and not in a follow-up period.

Panel 5 Treatment periods and exposure start and end

	Definition	
Time point	**Start**	**End**
Exposure	Date and time of the first dose as defined below for each treatment period.	Date and time of the end of the treatment periods as defined below.
Double-blind period	Date and time of the first dose in the trial	- Start of OL period -1 second, if exists - else **visit Week 16 date** (including unscheduled visits which has 107<=SVSTDY<=120) - else in case of **IMP discontinuation,** the latest of the date of **last dose** (1) + **14 days** and **ET date** (2) (ET assessments should be a part of the period they terminated in) - else the **date of the last contact**
Open-label period	Date and time of the dose taken at Week 16	- Visit **Week 32 date** - else in case of IMP discontinuation, the latest of the date of last dose (1) + 14 days and ET date (2) - else the date of the last contact, if not FUP
Safety follow-up period	Date of the end of the last treatment period	Date of last contact

Abbreviations: AE = adverse event, IMP = investigational medicinal product, SFU=safety follow-up

(1) The last dose is equal to 'Date of last administration of IMP' from 'End of Treatment' form in CRF.

(2) Only defined for subjects who have a reason for permanent discontinuation of IMP recorded.

5.4 Extent of exposure

Exposure time will be presented as patient years of exposure (PYE) and will be calculated as the difference between the exposure start date and time and the exposure end date and time and divided by 60×60×24×365.25 to convert from seconds to years. Exposure start date and time and exposure end date and time are defined in Panel 5. Exposure time will be summarized and listed based on the safety analysis set for the double-blind, open-label and entire treatment periods (where two treatment periods are combined) in 3 separate tables, using descriptive summary statistics for continuous data.

Patient years of follow-up will also be summarized using descriptive summary statistics for continuous data for the safety follow-up set.

For more details on derivation rules on exposure, see ADRG.

5.5 Intercurrent events (ICEs)

In this context, an ICE refers to a post-randomization event that either precludes the existence of or affects the interpretation of the measurements of the endpoint.

The following ICEs are defined to describe the treatment effect that is targeted with the different estimand strategies:

1. **Initiation of rescue treatment for AHE:**

   This ICE occurs when a subject initiates rescue treatment according to the definition of rescue treatment in Section 6.7.2 in the CPT. This ICE occurs at the discretion of the investigator.

2. **Initiation of treatment for AD:**

   This ICE occurs when a subject initiates rescue treatment for AHE according to the definition of rescue treatment for AHE in Section 6.7.2 in the CPT or when otherwise prohibited treatments are used to alleviate intolerable symptoms due to AD on other areas of the body than the hands and wrists (For more details, see ADRG). Allowed mild or moderate TCS and TCI for AD, as described in Section 6.7.3 in the CPT (Panel 7 in the CPT), will not be considered initiation of treatment for AD. This ICE occurs at the discretion of the investigator.

- **Permanent discontinuation of IMP due to lack of efficacy in AHE or adverse event:**

  This ICE occurs when a subject permanently discontinues IMP and the primary reason for discontinuation is reported as ‘adverse event’ or ‘lack of efficacy in AHE’.

- **Permanent discontinuation of IMP not due to lack of efficacy in AHE or adverse event:**

  This ICE occurs when a subject permanently discontinues IMP and the primary reason for discontinuation is reported as ‘death’, ‘lost to follow-up’, ‘pregnancy’, ‘withdrawal by subject’, or ‘other’. It can occur at the discretion of the subject, the investigator, or LEO Pharma, or if the subject is lost to follow-up.

- **Permanent discontinuation of IMP due to lack of efficacy in AD or adverse event:**

  This ICE occurs when a subject permanently discontinues IMP and the primary reason for discontinuation is reported as ‘adverse event’, ‘lack of efficacy in AHE’, or ‘lack of efficacy in AD on areas of the body other than hands and wrists. It can occur at the discretion of the subject, the investigator, or LEO Pharma. Discontinuation of IMP due to use of rescue medication for AD or due to lack of efficacy in AD are collected only as reason ‘Other’ (see CTP Section 7.2.1) with

'lack of efficacy in AD' as the primary reason for discontinuation entered as free text.

- **Permanent discontinuation of IMP not due to lack of efficacy in AD or adverse event:**

  This ICE occurs when a subject permanently discontinues IMP and the primary reason for discontinuation is reported as 'death', 'lost to follow-up', 'pregnancy', 'withdrawal by subject', or 'other' (excluding subjects indicating a 'lack of efficacy in AD on areas of the body other than hands and wrists'). It can occur at the discretion of the subject, the investigator, or LEO Pharma, or if the subject is lost to follow-up.

An overview of the strategies chosen to handle the ICEs for each estimand is provided in Panel 6 and Panel 7. Estimands to be considered when analyzing each endpoint for the overall or sub-group populations are presented in Panel 8.

Only the following three ICEs, in which the trial's target disease (i.e., AHE) is involved, are considered in the analyses of the AHE-related endpoints in this trial (See Panel 6):

- Initiation of rescue treatment for AHE
- Permanent discontinuation of IMP due to lack of efficacy in AHE or adverse event
- Permanent discontinuation of IMP not due to lack of efficacy in AHE or adverse event

And the following ICEs are considered in the analyses of EASI and DLQI, where AD is considered instead of AHE (See Panel 7):

- Initiation of treatment for AD
- Permanent discontinuation of IMP due to lack of efficacy in AD or adverse event
- Permanent discontinuation of IMP not due to lack of efficacy in AD or adverse event

For each of the two categories of AHE- and AD-related ICEs, the number and type of all three ICEs will be summarized by treatment group for the double-blind. The number and types of rescue medications for each of the AHE and AD categories will be presented by type and also by ATC level separately, and for the double-blind treatment period.

Time to permanent discontinuation of IMP by reason and time to withdrawal from the trial by reason will be presented in two separate figures for randomized subjects. Time to initiation of rescue treatment for AHE will be presented by type in figure for the double-blind treatment period for FAS. Time to initiation of the earliest in time occurring ICEs for AHE and time to initiation of the earliest in time occurring ICEs for AD will be presented in separate figures for the double-blind, based on the Aalen-Johansen estimator.

In case of multiple ICEs for a subject within one of the two categories (i.e. ICEs for AHE and ICEs for AD), the ICE with the earliest date or time will be counted and used when addressing intercurrent events in the statistical analysis of AHE or AD-related endpoints. In case of two ICEs for a subject in two separate categories, both will be presented in their corresponding category.

Aassessments which occur on the same day as some ICEs will not be affected by those ICEs. If multiple ICEs occur on the same day within each of the two categories, where no exact time of the occurrence is available, the ICE counted as the earliest in time will be determined following the order:

1) Rescue medication
2) Permanent discontinuation due to lack of efficacy in AHE/AD or adverse event
3) Permanent discontinuation not due to lack of efficacy in AHE/AD or adverse event

In all analyses, MAR and MNAR will be derived at a ‘subject’ level, i.e., presence of a specific ICE will determine whether missing data prior to the ICE and data after the ICE will be imputed as MAR or MNAR as specified in Section 5.6. Subjects with no ICE will be included in the MAR group. Only ICEs occurring in the double-blind period are relevant, as all estimand analyses are intended for the double-blind period.

Panel 6 Data handling strategies according to ICEs involved in the analyses of estimands associated with binary or continuous AHE-related endpoints

	Binary endpoints		Continuous endpoints	
	Primary estimand		Primary estimand	
ICE	**Estimand strategy**	**Missing value imputation method**	**Estimand strategy**	**Missing value imputation method**
Initiation of rescue treatment for AHE	**Composite**	All data after ICE are disregarded and considered as MNAR and the subject experiencing the ICE will be counted as a non-responder. (NRI)	**Hypothetical**	All data after ICE are disregarded and considered as MNAR and will be imputed using LOCF.
Permanent discontinuation of IMP due to lack of efficacy on AHE or adverse event	**Composite**	All data after ICE are considered as MNAR and the subject with the ICE will be counted as a non-responder. (NRI)	**Hypothetical**	All data after ICE are considered as MNAR and will be imputed using LOCF.
Permanent discontinuation of IMP not due to lack of efficacy on AHE or adverse event	**Hypothetical**	All data after ICE are considered as MAR and will be imputed (MI) using a Regression model.	**Hypothetical**	All data after ICE are considered as MAR and will be imputed (MI) using a Regression model.
No ICE	---	Missing data for subjects not experiencing an ICE will be considered as MAR and imputed (MI) using a Regression model. [(a)(b)]	---	Missing data for subjects not experiencing an ICE will be considered as MAR and imputed (MI) using a Regression model. [(a)(b)]

Abbreviations: AHE = atopic hand eczema; ICE = intercurrent event; IMP = investigational medicinal product; MI = multiple imputation; MAR = missing at random; MNAR = Missing not at random. LOCF = Last observation carried forward; NRI = non-responder imputation.
Notes:(a) MAR and MNAR records are derived at a 'subject' level, instead of the 'record'-level, where the ICE is considered and prioritized over a missing value due to other reasons than an ICE when specifying the affected subject as MAR or MNAR. Also, MAR and MNAR subjects are defined based on the double-blind treatment period and not the entire treatment period. (b) MAR subjects, no matter whether due to an ICE or other reason, will be imputed using the same Regression model. .

Panel 7 Data handling strategies according to ICEs involved in the analyses of estimands associated with binary or continuous EASI and DLQI endpoints

	Binary endpoints		Continuous endpoints	
	Primary estimand		Primary estimand	
ICE	**Estimand strategy**	**Missing value imputation method**	**Estimand strategy**	**Missing value imputation method**
Initiation of treatment for AD	**Composite**	All data after ICE are disregarded and considered as MNAR, and the subject experiencing the ICI will be counted as a non-responder. (NRI) [(a)]	**Hypothetical**	All data after ICE are disregarded and considered as MNAR and will be imputed using LOCF.
Permanent discontinuation of IMP due to lack of efficacy on AD or adverse event	**Composite**	All data after ICE are considered as MNAR, and the subject will be counted as a non-responder. (NRI) [(a)]	**Hypothetical**	All data after ICE are considered as MNAR and will be imputed using LOCF.
Permanent discontinuation of IMP not due to lack of efficacy on AD or adverse event	**Hypothetical**	All data after ICE considered MAR and will be imputed (MI) using a Regression model. [(b)]	**Hypothetical**	All data after ICE are considered as MAR and will be imputed (MI) using a Regression model.
No ICE	---	Missing data for subjects not experiencing an ICE will be considered as MAR and imputed (MI) using a Regression model. [(a)]	---	Missing data for subjects not experiencing an ICE will be considered as MAR and imputed (MI) using a Regression model. [(a)]

Abbreviations: AHE = atopic hand eczema; ICE = intercurrent event; IMP = investigational medicinal product; MI = multiple imputation; MAR = missing at random; MNAR = Missing not at random. LOCF = Last observation carried forward; NRI = non-responder imputation.
Notes: (a) MAR and MNAR records are derived at a 'subject' level, instead of the 'record'-level, where the ICE is considered and prioritized over a missing value due to other reasons than an ICE when specifying the affected subject as MAR or MNAR. Also, MAR and MNAR subjects are defined based on the double-blind treatment period and not the entire treatment period. (b) MAR subjects, no matter whether due to an ICE or other reason, will be imputed using the same Regression model.

Panel 8 Overview of estimand analyses for each endpoint

				Primary estimand for Binary endpoints		Primary estimand for continues endpoints		
Objective	**Type of endpoint**	**Endpoint**	**Type of estimand variable**	**Main Analysis**	**Sensitivity Analyses 1 and 2**	**Main analysis**	**Sensitivity Analysis 3**	**Efficacy Domain**
Primary (Efficacy)	Primary	IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 16.	Binary	Yes	Yes			IGA
Primary (Efficacy)	Secondary	Having a ≥2-point reduction in IGA-AHE score from baseline to Week 16.	Binary	Yes				IGA
Primary (Efficacy)	Key secondary	Having a decrease in HECSI of at least 75% (HECSI-75) from baseline to Week 16.	Binary	Yes				HECSI
Primary (Efficacy)	Key secondary	Having a decrease in HECSI of at least 50% (HECSI-50) from baseline to Week 16.	Binary	Yes				HECSI
Primary (Efficacy)	Key secondary	Having a decrease in HECSI of at least 90% (HECSI-90) from baseline to Week 16.	Binary	Yes				HECSI
Primary (Efficacy)	Key secondary	Percentage change in HECSI score from baseline to Week 16.	Continuous			Yes	Yes	HECSI
Secondary 1 (Efficacy)	Key secondary	Reduction in HESD itch score (weekly average) of ≥4 points from baseline to Week 16.	Binary	Yes				HESD
Secondary 1 (Efficacy)	Key secondary	Reduction in HESD pain score (weekly average) of ≥4 points from baseline to Week 16.	Binary	Yes				HESD
Secondary 1 (Efficacy)	Secondary	Percentage change in HESD itch score (weekly average) from baseline to Week 16.	Continuous			Yes		HESD
Secondary 1 (Efficacy)	Secondary	Percentage change in HESD pain score (weekly average) from baseline to Week 16.	Continuous			Yes		HESD

				Primary estimand for Binary endpoints		Primary estimand for continues endpoints		
Objective	**Type of endpoint**	**Endpoint**	**Type of estimand variable**	**Main Analysis**	**Sensitivity Analyses 1 and 2**	**Main analysis**	**Sensitivity Analysis 3**	**Efficacy Domain**
Secondary 1 (Efficacy)	Other/ exploratory	Reduction in HESD pain score (weekly average) of ≥3 points from baseline to Week 16	Binary	Yes				HESD
Secondary 1 (Efficacy)	Key secondary	Percentage change in HEIS score from baseline to Week 16.	Continuous			Yes		HEIS
Secondary 1 (Efficacy)	Other/exploratory	Percentage change in HEIS sleep score (weekly average) from baseline to week 16	Continuous			Yes		HEIS
Secondary 1 (Efficacy)	Key secondary	Percentage change in DLQI score from baseline to Week 16	Continuous			Yes		DLQI
Secondary 1 (Efficacy)	Other/ exploratory	Reduction in DLQI score of ≥4 points from baseline to Week 16.	Binary	Yes				DLQI
Other 1 (Efficacy)	Other/ exploratory	Percentage change in EASI score from baseline to Week 16	Continuous			Yes		EASI
Other 1 (Efficacy)	Other/ exploratory	Change in EASI score from baseline to Week 16	Continuous			Yes		EASI
Secondary 1 (Efficacy)	Secondary	Change in WPAI+CIQ:AHE domain scores from baseline to Week 16	Continuous			Yes		WPAI

5.6 Estimands analyses strategy

There are two types of estimands to be analysed in this trial, which are specified based on whether the endpoint's variable of interest is binary or continuous. Details of each of the two estimand analyses are described in this section and summarized in Panel 6, Panel 7 and Panel 8.

The estimands defined in this section applies in the analysis of all primary, secondary and exploratory endpoints defined for only the double-blind period, as specified in Panel 8, neither for the open-label period, nor for the entire treatment period.

The combination test, described in the following section, is used **only** for the analysis of the primary endpoint, i.e. 'IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 16', its corresponding tipping point and sub-group analyses, and the secondary endpoint of 'Having a ≥2-point reduction in **IGA-AHE** score from baseline to Week 16', using the primary estimand for binary endpoints (and also the sensitivity analyses 1 and 2) as described in Section 5.7.1.

Endpoints related to EASI and DLQI (with AD as the target disease) will use the same estimands as in the endpoints with AHE as the target disease, except for the ICEs 'initiation of rescue treatment for AHE' and "permanent discontinuation of IMP due to/not due to lack of efficacy on AHE or adverse event" being replaced by 'initiation of treatment for AD' and 'permanent discontinuation of IMP due to/not due to lack of efficacy on AD or adverse event' (see Panel 6 and Panel 7). Therefore, to avoid the repetition in the following sections, 'AHE/AD' is used wherever the only difference in ICEs is the target disease.

5.6.1 Primary estimand analysis for binary endpoints

5.6.1.1 Definition

- **Target population**: Subjects with moderate-to-severe AHE as defined by the eligibility criteria (CTP Sections 5.1 and 5.2).

- **Endpoint attribute**: Achievement of the endpoint of interest at Week 16 without initiation of 'rescue treatment for AHE/treatment for AD', or 'permanent discontinuation of IMP due to lack of efficacy in AHE/AD or adverse event' (composite strategy) in a hypothetical setting where permanent discontinuation of IMP due to other reasons would not occur (hypothetical strategy).

  - **Type of endpoint:** A binary variable

  - **ICEs involved:** As defined in Panel 6 and Panel 7.

5.6.1.2 Main statistical analysis:

For the ICEs 'initiation of rescue treatment for AHE/treatment for AD' and 'permanent discontinuation of IMP due to lack of efficacy in AHE/AD or adverse event', a 'composite' strategy will be applied; all data after the ICE are considered as MNAR, and subjects will be considered non-responders after the ICE occurred (NRI), reflecting an assumption that 'initiation of rescue treatment for AHE/treatment for AD' and 'permanent discontinuation of IMP due to lack of efficacy in AHE/AD or adverse event' indicates failure of the randomized treatment.

For the ICE 'permanent discontinuation of IMP not related to lack of efficacy in AHE/AD or adverse events', a 'hypothetical' strategy will be applied reflecting a scenario where all subjects remain on treatment, except those who permanently discontinue IMP due to lack of efficacy in AHE/AD or adverse event. Data collected after the occurrence of the ICE will be considered as MAR and imputed together with missing subject data not affected by an ICE using MI (full conditional specification (FCS), 100 iterations, seed=2328) assuming MAR within treatment group. Note that when imputing data for MAR patients, the data from patients with no ICE or no missing data will be utilized.

Note that all subject-level data observed prior to the occurrence of an intercurrent event will be used to inform the imputation models. Also, all missing values are imputed on the original continuous scale, if any, adjusting for treatment group, region, and baseline IGA, at the two preceding and two subsequent visits. Exceptions are imputation for those weeks for which the number of subsequent visits is reduced to one and zero, where only the available weeks will be used. The imputed continuous values will then be turned into the binary endpoint of interest. Negative imputed values will be set to zero, and values greater than the maximal possible value will be set to the maximum possible value.

The MNAR data will be combined with each of the 100 imputed MAR data to create 100 complete datasets. For each of the 100 complete datasets, the difference in response rates between the two treatment groups will be analysed using a logistic regression model adjusted for treatment group (reference=placebo), region (reference=North America), and baseline disease severity (reference = IGA-AHE score of 3). The estimates and standard errors of the marginal effect derived from each regression model using Bartlett method (1) will be combined using Rubin's rule to provide the estimate and associated standard error and p-value.

Only for the analysis of the primary endpoint, i.e. 'IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 16', its corresponding tipping point and sub-group analyses, and the secondary endpoint of 'Having a ≥2-point reduction in **IGA-AHE** score from baseline to Week 16', to account for the possible type I error inflation due to the adaptive design features, the inverse normal combination test will be applied, both in the interim and final analyses, combining the one-sided *p*-values p_1 and p_2 for the null hypothesis based on the subjects randomized 16 weeks prior to the cut-off date for interim analysis (referred to as the interim cohort) and the subjects randomized afterwards, by using the inverse weighted combination function

$$C(p_1, p_2) = 1 - \Phi\big(\omega_1 \Phi^{-1}(1 - p_1) + \omega_2 \Phi^{-1}(1 - p_2)\big) = 1 - \Phi(\widetilde{z_2})$$

with predefined equal weights of

$$\omega_1 = \omega_2 = \sqrt{0.5}.$$

Here

$$\widetilde{Z_2} = \omega_1 Z_1 + \omega_2 Z_2,$$

denotes the test statistics for combined *p*-value with $Z_1 = \Phi^{-1}(1 - p_1)$ and $Z_2 = \Phi^{-1}(1 - p_2)$ being the test statistics up to and after the interim analysis. Φ^{-1} denotes the inverse of the standard normal cumulative distribution function Φ.

A 95% confidence interval for the treatment difference between tralokinumab and placebo will be presented and derived by confidence testing based on the inverse normal combination test. The confidence interval will be constructed by testing the hypothesis that the treatment difference is equal to a specific value $\tilde{\mu}$ for all possible values of $\tilde{\mu}$. If the hypothesis is rejected, $\tilde{\mu}$ is not included in the confidence interval. The estimated treatment difference will be the center of the confidence interval. Individual treatment estimates along with 95% confidence intervals will also be derived by confidence testing.

More specifically, when deciding whether $\tilde{\mu}$ is included in the confidence interval, the following algorithm is used. Let d_1 be the treatment difference observed at the interim (i.e. based on the data collected prior to the interim) and let σ_1^2 be the variance of d_1. Similarly let d_2 and σ_2^2 be the treatment difference and variance for the data collected after the interim. The combined z statistic then becomes

$$z_{comb} = \sqrt{0.5}\,\frac{d_1}{\sigma_1} + \sqrt{0.5}\,\frac{d_2}{\sigma_2}.$$

When testing whether $\tilde{\mu}$ is included in the confidence interval, the z-value,

$$z_{comb,\tilde{\mu}} = \sqrt{0.5}\,\frac{d_1 - \tilde{\mu}}{\sigma_1} + \sqrt{0.5}\,\frac{d_2 - \tilde{\mu}}{\sigma_2},$$

will be testing against the hypothesis of $\mu = \tilde{\mu}$, by solving the two equations

$$\sqrt{0.5}\,\frac{d_1 - \tilde{\mu}}{\sigma_1} + \sqrt{0.5}\,\frac{d_2 - \tilde{\mu}}{\sigma_2} = \pm 1.96.$$

If the hypothesis is rejected $\tilde{\mu}$ will not be included in the confidence interval. 1-sided tests in both directions with an alpha of 0.025 will be used to construct a 2-sided 95% confidence interval. The same approach using the logit function will be used to construct individual treatment estimates and confidence intervals.

5.6.2 Primary estimand analysis for continuous endpoints

5.6.2.1 Definition

- **Target population**: Subjects with moderate-to-severe AHE as defined by the eligibility criteria (CTP Sections 5.1 and 5.2).

  - **Endpoint attribute**: Change from baseline in endpoint of interest in a hypothetical setting where permanent discontinuation of IMP or use of rescue treatment for AHE/treatment for AD would not occur (hypothetical strategy).

  - **Type of endpoint:** A continuous variable

  - **ICEs involved:** As defined in Panel 6 and Panel 7.

5.6.2.2 Main statistical analyses:

For the ICEs ‘initiation of rescue treatment for AHE/treatment for AD’ and ‘permanent discontinuation of IMP due to lack of efficacy on AHE/AD or adverse event’, a ‘hypothetical’ strategy will be applied; all data after the ICE are considered as MNAR, and subjects will be imputed using the LOCF, reflecting the assumption that these subjects are not expected to improve the efficacy more than the last observed status going forward if they had continued staying on the IMP.

For the ICE 'permanent discontinuation of IMP not related to lack of efficacy on AHE/AD or adverse events', a 'hypothetical' strategy will be applied reflecting a scenario where all subjects remain on treatment except those who permanently discontinue IMP due to lack of efficacy in AHE/AD or adverse event. Data collected after the occurrence of the ICE will be considered as MAR and imputed together with missing data not affected by an ICE using MI (full conditional specification (FCS), 100 iterations, seed=2328) assuming MAR within treatment group, and adjusting for treatment group (reference=placebo), region (reference=North America), and baseline disease severity (reference = IGA-AHE score of 3). Note that when imputing data for MAR patients, the data from patients with no ICE or no missing data will be utilized.

Note that all subject-level data observed prior to the occurrence of an intercurrent event will be used to inform the imputation models. Negative imputed values will be set to zero, and values greater than the maximal possible value will be set to the maximum possible value.

The MNAR data will be combined with each of the 100 imputed MAR data to create 100 complete datasets. Each of the 100 complete datasets will be analyzed using an ANCOVA model adjusted for the effect of treatment group, region, baseline IGA-AHE score, and baseline value (endpoint of interest). Then, the estimates and standard errors of the marginal effect derived from each regression model will be combined using Rubin's rule to provide the estimate and associated standard error and p-value.

5.7 Sensitivity analyses

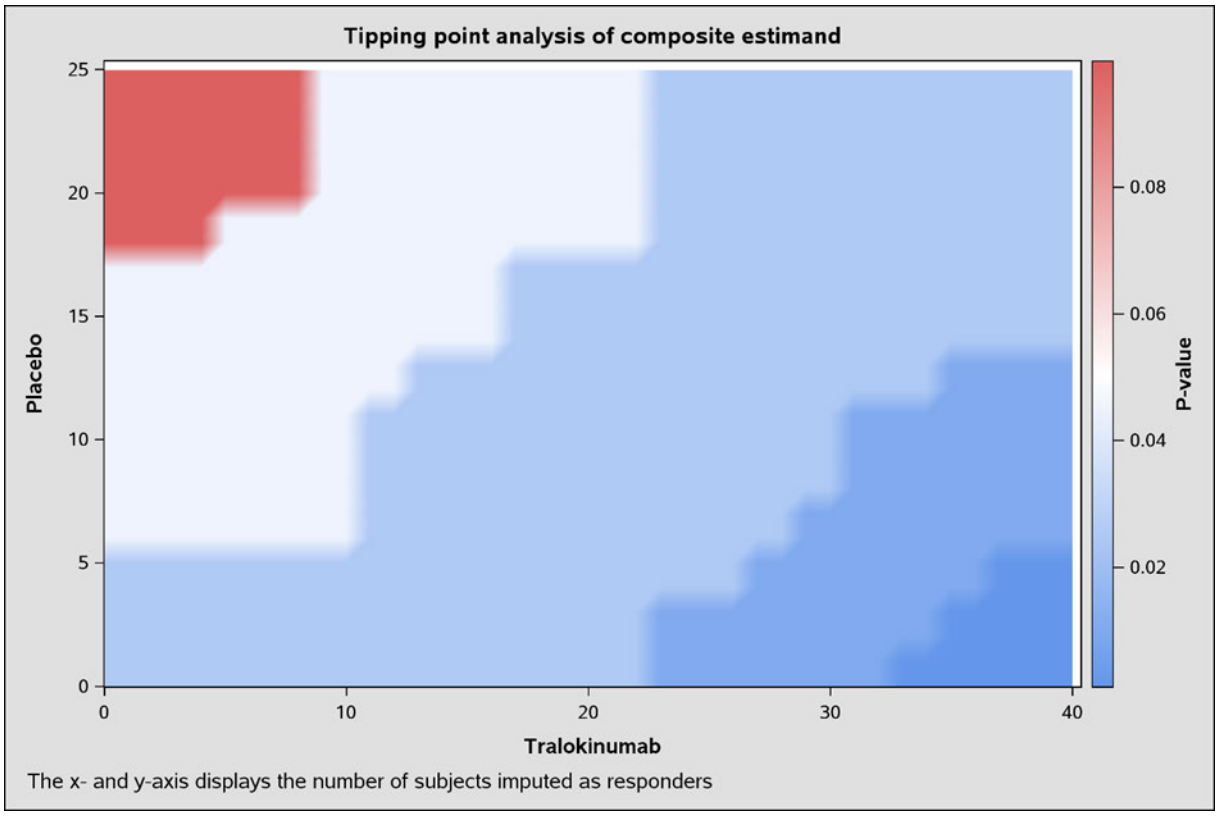
5.7.1 Sensitivity analysis 1: tipping point analysis for the primary binary endpoint

To evaluate the robustness of the multiple imputation of missing data and the MAR assumption only for the primary endpoint, i.e., IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 16, a tipping point analysis will be performed based on the primary analysis using the combination test. Missing data for subjects who did not initiate rescue medication or discontinue IMP due to lack of efficacy on AHE or adverse event prior to the Week 16 visit, will be handled as follows:

- Let N_t and N_p be the number of subjects imputed by multiple imputation (i.e., subjects who permanently discontinued IMP not due to lack of efficacy in AHE or adverse event prior to the Week 16 visit and subjects with missing data at Week 16, who did not experience an ICE prior to the Week 16 visit) in the tralokinumab and placebo group, respectively.
- Let X be the number of subjects in the tralokinumab group imputed as responders (X is a number between 0 and N_t). Thus $N_t - X$ is the number of subjects imputed as non-responders in the tralokinumab group.

- Let Y be the number of subjects in the placebo group imputed as responders (Y is a number between 0 and N_p). Thus $N_p - Y$ is the number of subjects imputed as non-responders in the placebo group.
- All possible combinations of X and Y will be analyzed for the primary endpoint as follows: For each of the $N_t + N_p$ subjects in scope for the sensitivity analysis, the possible outcome is either response or non-response, giving a total of $2^{N_t+N_p}$ possible complete datasets. Each complete dataset will be analyzed for the primary endpoint using the inverse normal combination test as described in the CTP Section 9.3.2.3. For each combination of X and Y, the average p-value will be calculated among all possible complete datasets with X subjects imputed as responders in the tralokinumab group and Y subjects imputed as responders in the placebo group.
- The *p*-values for the one-sided test of difference in proportion of responders in tralokinumab versus placebo for each combination of responders in the two groups are displayed in a heatmap (example is shown in Panel 20 in the CTP for a 2-sided test with X up to 40 and Y up to 25. The bottom-right part of the map in blue represents the combinations of responders leading to rejection of the null hypothesis, whereas the upper-left part colored in red represents the combinations where we cannot reject the null hypothesis. The white area represents the tipping points).

Panel 9 Tipping point analysis of composite estimand (an example)



5.7.2 Sensitivity analysis 2: Relative weights in the combination test for the primary binary endpoint

This sensitivity analysis is a variation of the primary analysis of the primary endpoint, using different weights in the combination test. Instead of equal weights of $\sqrt{0.5}$, relative weights proportional to sample sizes in the two pre- and post-interim cohorts of subjects will be used, i.e., $\omega_i = \sqrt{n_i/(n_1 + n_2)}$ for $i = 1, 2$, where n_i is the sample size for cohort i.

5.7.3 Sensitivity analysis 3: tipping point analysis for the continuous key secondary endpoint

A tipping point analysis will be performed only for the key secondary endpoint of 'Percentage change in HECSI score from baseline to week 16' based on implementation of a delta-adjusted multiple imputation approach with the purpose of assessing the robustness of the results of the main analytical approach with respect to the varying departures from the MAR assumption within each treatment group.

The delta-adjusted imputation approach allows for missing data to be imputed under a MNAR assumption. Heuristically, the imputation strategy shifts the parameters of the MAR distribution

based on the value of a numeric offset term (Δ). The tipping point analysis will adjust the values of the parameters in the MAR distribution, representing the mean change in endpoint parameter from baseline to Week 16.

The range of the Δ parameter for both treatment groups will be decided after the interim analysis 2 unblinding to ensure a meaningful analysis. The seed will be 2328.

5.8 Subgroup analyses

Four sub-group analyses will be performed based on baseline EASI scores, as defined in the following:

- **Sub-group 1:** Subjects with a baseline EASI score greater than 7, indicating moderate to severe AD, comprising approximately 40% of the population.
- **Sub-group 2:** Subjects with a baseline EASI score greater than 7 but less than 16, comprising approximately 25% of the population
- **Sub-group 3:** Subjects with a baseline EASI score greater than or equal to 16, indicating moderate to severe AD and candidates for systemic therapy, comprising approximately 15% of the population
- **Sub-group 4:** Subjects with a baseline EASI score less than or equal to 7, indicating mild AD

The endpoints defined in Panel 10 will be analysed and tabulated based on the corresponding estimand defined in Section 5.6, only if there is enough number of subjects for meaningful analyses, considering that arms are not balanced w.r.t EASI scores at baseline. Otherwise, descriptive analyses presenting summary statistics will be performed. Endpoints defined for sub-group analyses which are not among the endpoints defined in the protocol will be also analyzed for the overall population.

Panel 10 Endpoints for sub-group analyses

Endpoint	Overal population	Sub-groups 1,2,3 (3 separate outputs)	Sub-group 4
IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 16	Yes	Yes	Yes
Having EASI score of3 or less at Week 16	Yes	Yes	-----
Having EASI score of 7 or less at Week 16	Yes	Yes	-----
Change in EASI score from baseline at Week 16	Yes	Yes	Yes
Percentage change in EASI score from baseline at Week 16	Yes	Yes	Yes
Having a decrease in EASI of at least 50% (EASI-50) from baseline at Week 16	Yes	Yes	Yes
Having a decrease in EASI of at least 75% (EASI-75) from baseline at Week 16	Yes	Yes	Yes
Having a decrease in EASI of at least 90% (EASI-90) from baseline at Week 16	Yes	Yes	Yes
AESIs – Eye disorders by SOC and PT during the double-blind period	Yes	Yes	Yes

5.9 Pharmacokinetics (PK) analysis

Not applicable.

5.10 Pharmacodynamics and pharmacogenomics analysis

Not applicable.

5.11 Safety analysis

The analysis of safety will be presented separately for the double-blind and open-label treatment and safety follow-up periods.

Details on incomplete dates, duplicate measurements, unscheduled visits can be found in the ADRG or Define.xml.

The analysis of safety will be based on the safety analysis set corresponding to the trial period (see Panel 4).

5.11.1 Adverse events

AEs will be coded during the course of the trial according to Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 and presented by preferred terms (PT) within primary system organ class (SOC).

An event will be considered treatment-emergent if started after the first use of IMP or if started before the first use of IMP and worsened in severity after first dose of IMP. The tabulations described in the following will only include the TEAEs. Outputs will as a minimum present AEs, most frequent AEs (incidence ≥5%), AEs with possible or probable relation to IMP, Fatal AEs, SAEs, AEs leading to withdrawal or permanent discontinuation, AESIs and AEs by severity.

Evaluation of events will be based on number of subjects, number of subjects with events, percent of subjects with events, number of events and rate of events per 100 subject years of observation. . The overview of AEs will include the following information: seriousness, severity, relatedness, outcome, action to trial product (interventions). Forest plots will be presented for key tables.

Listings will as a minimum be provided for: AEs, Severe AEs, AEs with fatal outcome, SAEs, Non-TEAEs, AEs leading to permanent discontinuation of IMP and/or withdrawal, AESIs, Other events, AEs originating from other events involving IMP. AEs for which narratives will be provided are described in CTP Appendix 2, Section 10.2.6 .

The AEs listed in Panel 11 are considered adverse events of special interest (AESIs) in this trial and will have additional details recorded in the eCRF.

Panel 11 Adverse events of special interest

Adverse event of special interest	Additional data to be recorded	Data collection method
Conjunctivitis	• Unilateral/bilateral. • Etiology (allergic[a], atopic[b], viral, bacterial, other (please specify), unknown). • If infectious etiology, was it confirmed by laboratory testing. • Diagnosis confirmed by ophthalmologist.	eCRF
Keratoconjunctivitis	• Unilateral/bilateral. • Etiology (atopic, vernal, viral, bacterial, other (please specify), unknown). • If infectious etiology, was it confirmed by laboratory testing. • Diagnosis confirmed by ophthalmologist.	eCRF
Keratitis	• Unilateral/bilateral. • Etiology (allergic, viral, bacterial, other (please specify), unknown). • If infectious etiology, was it confirmed by laboratory testing. • Diagnosis confirmed by ophthalmologist.	eCRF

a. Allergic conjunctivitis: acute and episodic associated with tearing, sneezing, and runny nose.
b. Atopic conjunctivitis associated with eyelid/facial eczema and dry eyes.

5.11.2 Vital signs

Vital signs are tabulated as described in the CTP Section 9.3.5.2. In addition, vital signs will be summarized by protocol defined visit week, and a shift table will be produced for vital signs showing ‘low’, ‘normal’, and ‘high’ categories at baseline against those at the end of the treatment period. The normal ranges for this classification are provided in Panel 12.

Panel 12 Normal ranges to be used for shift tables involving vital signs parameters

Parameter	Normal range
Body temperature	36˚C - 38˚C
Diastolic Blood Pressure	50 mmHg – 105 mmHg
Systolic Blood Pressure	90 mmHg – 180 mmHg
Pulse	50 beats/min – 120 beats/min

5.11.3 Physical examination

Only abnormal findings at screening will be listed.

5.11.4 Clinical laboratory evaluation

Panel 13 describes the clinical laboratory tests performed in the trial. For the laboratory parameters collected post-baseline, the observed change from baseline to Week 16/32 will be summarized by treatment group and visit, using mean, SD, median, 1st quartile, 3rd quartile, minimum, and maximum values. ALT, AST, BILI, thrombocytes, and white blood cells (neutrophils, lymphocytes, monocytes, basophils, and eosinophils) are measured at screening, week 8, week 16, and week 32. Other laboratory parameters are only measured at screening and will be only listed.

For liver parameters (ALT, AST, and BILI,) and white blood cells (neutrophils, lymphocytes, monocytes, basophils, and eosinophils), the guideline or literature defined thresholds in Panel 13 will be used for producing shift tables and categorical threshold tables.

The remaining laboratory parameters will be classified as ‘low’, ‘normal’, or ‘high’, depending on whether the value is below, within, or above the reference range and these categories will be used for producing shift tables, except for the serology parameters for which the classifications used in the outputs has been specified in Panel 13.

If any subjects have concurrent elevations of ALT, AST, and BILI, per the guideline- or literature-defined thresholds, an individual profile plot of the subjects’ ALT, AST, and BILI over the trial period will be provided.

For laboratory parameters, the values collected at the screening visit will be used as baseline values.

Panel 13 Clinical laboratory tests and their thresholds

Chemistry	Thresholds used for the classifications in outputs
Liver and renal parameters: Aspartate aminotransferase (AST) - Liver Alanine aminotransferase (ALT) - Liver Creatinine[a] - Kidney Alkaline phosphatase[a] (ALP) - Liver Gamma glutamyl transferase[a] Bilirubin[b]	Thresholds and ranges in TMF-000856894
Electrolytes and glucose: Sodium[a] Potassium[a] Calcium[a]	Low', 'Normal', or 'High'
Lipid parameters: Cholesterol[a] LDL cholesterol[a] HDL cholesterol[a] Triglycerides[a]	Low', 'Normal', or 'High'
Hematology[d]	
Thrombocytes Erythrocytes[a] Hemoglobin[a]	Low', 'Normal', or 'High'
White blood cells: Leukocytes Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Thresholds and ranges in TMF-000856894
Serum pregnancy test[a,c]	
Choriogonadotropin beta	'Negative', 'Positive'
Serology[a,d]	
Hepatitis B virus surface antigen Hepatitis B virus surface antibody Hepatitis B virus core antibody Hepatitis C virus antibody HIV-1 antibody HIV-2 antibody	- For Hepatitis B and HIV measures: "Reactive', 'Non Reactive', Grayzone'. - For Hepatitis C Virus RNA: 'Not Detected', 'Detected' (not done for all subjects)

Abbreviations: HDL = high density lipoprotein; HIV = human immunodeficiency virus; LDL = low density lipoprotein.

a. Collected at screening only.
b. If bilirubin is above upper limit of normal, direct and indirect bilirubin will also be measured.
c. Only women of childbearing potential.
d. If it is necessary to re-test or to perform additional tests to support the result of the initial test , these will be performed by the central laboratory.

5.12 Interim analyses

The term ‘interim analysis’ refers to any ‘prospectively planned’ analysis in the middle of the trial, irrespective of performing an associated DBL. In this trial, there are two interim analyses.

5.12.1 Interim analysis 1 for sample-size re-evaluation

As a part of the adaptive design of the trial, the sample size was re-evaluated at an unblinded interim evaluation of only the primary endpoint, by an independent unblinded statistician. The interim analysis was performed based on data with the cut-off date 23-Oct-2024. The smallest sample size required to achieve a conditional power of 90% was re-calculated to be 229.

Roles and responsibilities of the unblinded independent external statistician together with the blinded LEO Pharma functions during the interim process (i.e., before interim, at the interim, and after interim) and some more details including a timeline were specified in an Interim Charter, which was approved before the interim analysis dated 17-Oct-2024 (TMF-000930309).

Only the new sample size, which is a single number was shared with the blinded trial team. No outputs/TFLs were created based on this result. Blinding considerations during the interim process was described in the Blinding Plan, Version 1, dated 30-Apr-2024 (TMF-000884852). Statistical details can be found in the Interim Charter and Section 5.6.

Week 16 data for evaluable subjects was as clean as possible before unblinding data to ensure data integrity.

5.12.2 Interim analysis 2 at the end of the double-blind treatment period

The 2nd interim analysis will be performed when all subjects enrolled have had their Week 16 visit or early termination visit and will include all analyses planned for the double-blind treatment period. All primary and secondary endpoints are analysed in this interim analysis.

Note that Week 16 data will be cleaned before unblinding data to ensure data integrity.

6 Changes to analyses described in the protocol

Panel 14 summarises the changes to the analyses planned in the protocol.

Panel 14 Changes to protocol

Section in CTP	Description of change	Brief rational
9.2	Period-specific analysis sets were added.	Analysis sets added to make sure that only subjects contributing with exposure in the specific period are used in tabulations for the specific period.
9.3.5.3	As the majority of the laboratory values are only measured at screening, tables showing the change to week 16 are only created for AST, ALT, thrombocytes, and white blood cells. Therefore, other measures mentioned in the protocol were removed from the SAP.	To align with the CTP.
9.3 and 3	Method for imputing data after the ICEs 'initiation of rescue treatment for AHE/treatment for AD' and 'permanent discontinuation of IMP due to lack of efficacy for AHE/AD or adverse event' was changed from MI to LOCF.	To align with the estimand strategy for the binary endpoints, where the composite strategy for these ICEs are used to reflect that this is interpreted as failure to treatment.
9.3.1.1.	In the protocol, it was written that number and type of ICEs will be summarized by treatment group and visit. They will not be presented by 'visit'.	Not deemed to add additional relevant information.

Section in CTP	Description of change	Brief rational
9.3.5.2	Shift tables for vital signs will be presented for all values, and not only for the clinically significant abnormal values.	Information about abnormality and clinically significancy is not collected in the CRF.
9.3	The decisions regarding inclusion/exclusion of subjects or subject data in the trial analysis sets will only be documented before breaking the randomization code for the interim analysis at the end of the double-blind period and, if needed, for the final analysis, but not for the interim analysis for sample size re-evaluation.	Not deemed to be necessary for the sample size re-calculation.

7 Supporting documentation

The scoring algorithm for WPAI:SHP is provided in the following section. Any further details and agreements about clinical outcomes are documented in the ADRG.

7.1 Scoring algorithm for WPAI:SHP v2.0

The WPAI:SHP score for each of the 4 domains (absenteeism, presenteeism, work productivity loss and activity impairment) reflects the percentage impairment due to SHP during the past 7 days, ranging from 0 to 100 with higher numbers indicating greater impairment and less productivity, i.e. worse outcomes.

The WPAI:SHP domain scores will be derived as:

- **Absenteeism score:** If Q1 = Yes and Q2 + Q4 > 0, and Q2 and Q4 are not missing, then calculate the percentage of work time missed due to SHP
    - Q2/(Q2+Q4)*100
- **Presenteeism score:** If Q1 = Yes and Q5 is not missing, then calculate the percentage of reduced productivity while at work due to SHP.
    - Q5/10*100
- **Work productivity loss score:** If Q1 = Yes and Q2 + Q4 > 0, and Q2, Q4, and Q5 are not missing, then calculate the percentage of overall work impairment due to SHP.
    - (Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)])*100
- **Activity impairment score:** If Q6 is not missing, then calculate the percentage of impairment in daily activities outside of work due to the health condition
    - Q6/10*100

For further details refer to: http://www.reillyassociates.net/WPAI_Scoring.html.

In case a domain score cannot be calculated as described above, the domain score will be set as missing.

Questions:

Q1 = currently employed
Q2 = hours missed due to specified problem

Q3 = hours missed other reasons

Q4 = hours actually worked

Q5 = degree problem affected productivity while working

Q6 = degree problem affected regular activities

8 References

1. Bartlett JW. Covariate adjustment and estimation of mean response in randomised trials. Pharm Stat. 2018;17(5):648-666.

2. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4(5):353-365.

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Reason for signing: Approved	Manage Name: PPD Capaci PPD Date of sig 26-May-2025 12:58:48 GMT+0000

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