Statistical Analysis Plan

LP0162-1338

Efficacy and safety of tralokinumab administered by an autoinjector in adults and adolescents with moderate-to-severe atopic dermatitis

INJECZTRA

Design of trial:

Phase 3 efficacy and safety of tralokinumab administered by an autoinjector

An open-label, single-arm, phase 3 trial to evaluate the efficacy and safety of tralokinumab administered by an autoinjector in subjects with moderate-to-severe atopic dermatitis

LEO Pharma A/S	**Trial ID:**	**LP0162-1338**
	Date:	**26-Apr-2023**
	Version:	**2.0**

TMF-000662267 - Version 2.0

TMF-000897174 - Version 1.0

Statistical analysis plan statement

Approval statement, LEO Pharma A/S

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:

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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 abbreviations

AE	adverse event
AESI	adverse event of special interest
AD	atopic dermatitis
ADA	anti-drug antibodies
ADaM	Analysis Data Model
ADRG	analysis data reviewer's guide
ASDD	analysis set definition document
ATC	Anatomic Therapeutic Chemical Classification
BSA	body surface area
CDISC	Clinical Data Interchange Standards Consortium
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
COVID-19	coronavirus disease 2019
CTP	clinical trial protocol
CTR	clinical trial report
DBL	database lock
Define.xml	data definition document
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI75	at least 75% reduction in EASI score from baseline
EASI50	at least 50% reduction in EASI score from baseline
EASI90	at least 90% reduction in EASI score from baseline
eCRF	electronic case report form
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome
FAS	full analysis set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	investigator's Global Assessment
IMP	investigational medicinal product

ISR	injection site reaction
MedDRA	Medical Dictionary for Regulatory Activities
nAb	neutralising antibodies
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
POEM	Patient-Oriented Eczema Measure
PRO	patient-reported outcome
PT	preferred term
PYE	patient years of exposure
Q2W	every other week
SAE	serious adverse event
SAF	safety analysis set
SAS	Statistical Analysis Software
SC	subcutaneous(ly)
SD	standard deviation
SFU	safety follow-up
SOC	system organ class

Version history

The statistical analysis plan (SAP) for trial LP0162-1338 is based on the clinical trial protocol (CTP) version 3.0 dated 24-Aug-2022.

SAP version	Date	Change	Rationale
1.0	13-Feb-2023	Not applicable	Original version
2.0	26-Apr-2023	Include entire trial period for all adult subjects in the interim analysis	Scope of interim analysis changed

1 Introduction

The statistical analysis will be performed as outlined in the CTP version 3.0. This SAP, prepared before database lock, 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/summarised in Section 6, while supplementary analysis specifications are elaborated in the 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).

1.1 Trial objectives, estimands, and endpoints

Objectives	Endpoints
Primary objective	
To evaluate the efficacy of tralokinumab administered by an autoinjector when used to treat subjects with moderate-to-severe AD.	**Primary endpoints** • IGA score of 0 (clear) or 1 (almost clear) at Week 16. • EASI75 at Week 16.
Secondary objective	
To evaluate the safety and tolerability of tralokinumab administered by an autoinjector when used to treat moderate-to-severe AD.	**Secondary endpoints** • Number of treatment-emergent AEs from baseline to Week 16. • Presence of treatment-emergent ADA from baseline to Week 16.
Other objectives	
To assess the real-life patient handling experience with the use of tralokinumab administered by an autoinjector in patients with moderate-to-severe AD.	**Other endpoints** • Successful IMP self-administration when observed at the clinic at Week 4. • Successful IMP self-administration when administered at home at Week 8.
To evaluate the efficacy of tralokinumab administered by an autoinjector on severity and extent of AD, itch, and HRQoL in treating moderate-to-severe AD.	**Other endpoints** • EASI90 at Week 16. • EASI50 at Week 16. • Percentage change in EASI score from baseline to Week 16. • Change in POEM from baseline to Week 16. • Reduction in POEM of at least 4 from baseline to Week 16[1,2]/Reduction in POEM of at least 6 from baseline to Week 16[1,2]. • Change in DLQI/CDLQI from baseline to Week 16. • Reduction in DLQI of at least 4 from baseline to Week 16[1,2]/Reduction in CDLQI of at least 6 from baseline to Week 16[1,2]. • Change in Eczema-related Weekly Sleep NRS from baseline to Week 16. • Change in Worst Weekly Pruritus NRS/Adolescent's Pruritus NRS from baseline to Week 16. • Reduction of Worst Weekly Pruritus NRS/Adolescent's Pruritus NRS of at least 4 from baseline to Week 16[3].

1. Only adult subjects with a score of 4 and above and adolescent subjects with a score of 6 and above at baseline will be included in the analysis.
2. For adult subjects, a response is defined as a reduction of at least 4 from baseline. For adolescent subjects, a response is defined as a reduction of at least 6 from baseline.
3. Only subjects with Worst Weekly Pruritus NRS/Adolescent's Pruritus NRS score of 4 or above at baseline will be included in the analyses.

Abbreviations: AD = atopic dermatitis; ADA = anti-drug antibodies; AEs = adverse events; CDLQI =Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI90/EASI75/EASI50 = at least 90% / 75% / 50% reduction in EASI score; HRQoL = health-related qualify of life; IGA = Investigator's Global Assessment; IMP = investigational medicinal product; NRS = numeric rating scale; POEM = Patient-Oriented Eczema Measure.

The primary endpoints will be analysed using a composite estimand strategy to handle the occurrence of two intercurrent events considered to affect the interpretation of the estimates of the endpoints (initiation of rescue medication and permanent discontinuation of IMP).

The composite estimand evaluates the response rate without initiation of rescue treatment or permanent discontinuation of IMP. For subjects who received rescue treatment prior to Week 16 or who have permanently discontinued IMP prior to Week 16, observed data after the intercurrent events will be considered non-response, reflecting an assumption that initiation of rescue treatment or permanent discontinuation of IMP indicates either failure of the treatment to achieve response or that a possible positive response is not attributable to the treatment alone. Missing data for subjects who do not attend the Week 16 visit and where rescue medication has not been used, nor the subject has permanently discontinued IMP, will be imputed as non-response.

1.2 Trial design

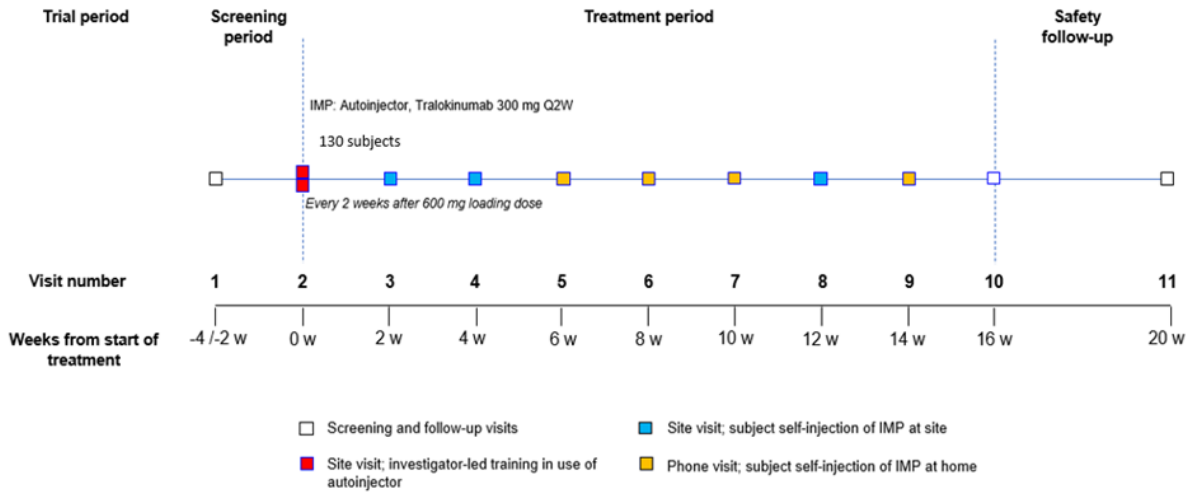
This is an open-label, single-arm, phase 3 trial, in adult and adolescent (age 12 to 17 years) subjects with moderate-to-severe AD. The trial is designed to evaluate the efficacy and safety of tralokinumab administered by an autoinjector. The trial design is illustrated in Panel 1.

The trial will consist of a 2- to 4-week screening period, a 16-week treatment period, and a 4-week safety follow-up period.

Approximately 130 subjects, of which approximately 30 subjects will be adolescents are planned to be assigned to the treatment. The trial will be conducted at approximately 30 sites in US. The anticipated average number of subjects assigned to treatment per trial site is 4.

For details on trial design, see Section 7 of the CTP.

Panel 1: Trial design



Approximately 130 subjects, of which approximately 30 subjects will be adolescents are planned to be assigned to the treatment.
Abbreviations: IMP = investigational medicinal product; Q2W = every other week; w = weeks.

An interim CTR including only adult subjects will be made to support submission for marketing approval of tralokinumab. The interim analysis will be based on data collected for adult subjects during the trial period and performed after interim database lock (DBL).

The primary analysis based on 100% data availability and all subjects (adults and adolescents) will be performed after DBL.

2 Testing strategy

There will be no formal testing.

3 Sample size

Sample size documentation is provided in the CTP Section 14.1.

Approximately 130 subjects of whom approximately 30 are adolescents, will be assigned to treatment.

4 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All subjects assigned to treatment and who received at least 1 dose of IMP will be included in the full analysis set (FAS) and the safety analysis set (SAF). Exclusions from the FAS can be considered in special cases as described in ICH E9, Section 5.2.1., Full Analysis Set. If it is decided to exclude a subject who has received IMP from the FAS, a justification addressing ICH E9 will be given.

The decisions regarding inclusion/exclusion of subjects or subject data from the trial analysis sets will be documented in the analysis set definition document ASDD (TMF-000811745).

For the purposes of analysis, the definition of the analysis sets are listed in Panel 2**.**

Panel 2: Trial analysis sets

Trial analysis set	Description and purpose
Full analysis set (FAS)	• All subjects assigned to treatment and who received at least 1 dose of IMP. • The FAS is used to analyse endpoints related to the efficacy objectives
Safety analysis set (SAF)	• All subjects assigned to treatment and who received at least 1 dose of IMP. • The SAF is used to analyse the endpoints and assessments related to safety, PK and ADA during the treatment period.
Usability analysis set	• All subjects assigned to treatment, who received at least 1 dose of IMP and have been trained in the usage of the autoinjector by investigator or delegated staff at the baseline visit. • Usability analysis set will be used to analyse objectives related to subject self-administration.
Safety follow-up (SFU) analysis set	• All subjects for whom date of last contact is after the date of exposure end, where exposure end is defined as the date of week 16 visit for subjects completing the treatment period, and otherwise the date of permanent discontinuation of IMP for subjects not completing the treatment period. • SFU analysis set is used to analyse endpoints and assessments related to safety during the SFU period.

Abbreviations: IMP = investigational medicinal product

5 Statistical analysis

5.1 General principles

The first day of dosing is considered baseline (Week 0, Visit 2).

All CIs will be presented with 95% degree of confidence, unless otherwise specified. The Wilson method is used to calculate the CI for the binary endpoints, and the statistically method Student's t-CI is used to calculate the CI for the continuous endpoints.

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

Categorical data will be summarised using the number and percentage of subjects in each category. Continuous data will be summarised using the mean, standard deviation (SD), median, 1st quartile, 3rd quartile, minimum, and maximum values.

5.1.1 Missing values

Missing baseline values will not be imputed, meaning that such subjects will be excluded from analyses concerning change from baseline as this cannot be derived. Unless otherwise specified, the baseline value is defined as the latest pre-dose assessment.

Procedures for handling missing values that are not baseline values are included in the sections describing the individual analyses.

Analysis of PK parameters will only include samples that are available, i.e. missing values will not be imputed.

5.1.2 Trial periods and date of permanent discontinuation of IMP

The treatment period will be defined as the time from exposure start to exposure end and the remaining time after exposure end will be defined as the safety follow-up period. SFU period is only applicable for subjects where last date of contact does not equal the date of exposure end.

Definition of date of permanent discontinuation of IMP, exposure start, and exposure end are given in Panel 3.

Panel 3: Date of permanent discontinuation of IMP, exposure start and end

Time point	Definition
Date of permanent discontinuation of IMP*	• Defined as the latest date of early termination visit (if existing) or date of onset of latest AE leading to withdrawal of IMP, otherwise date of the last visit, excluding SFU visit.
Exposure start	• Date and time of first dose.
Exposure end	• Date of Week 16 visit (if existing) at time 23:59:00, otherwise date of permanent discontinuation of IMP (if existing) at time 23:59:00, otherwise date of last IMP administration at time 23:59:00.

*) Only defined for subjects who have a reason for permanent discontinuation of IMP recorded.
Abbreviations: AE = adverse event, IMP = investigational medicinal product, SFU=safety follow-up

5.1.3 Treatment and trial completers

A subject who has not permanently discontinued IMP before Week 16 will be defined as a treatment completer.

A subject is considered to have completed the trial if they have completed all periods of the trial including the safety follow-up visit (Week 20).

5.1.4 Early termination and unscheduled visits

When no data are available from a certain scheduled post-baseline visit for a subject, data from early termination visits and unscheduled visits may replace data from that scheduled visit in data summaries, provided the data are collected between 6 days before and 7 days after the planned time point for the scheduled visits, as given in Panel 4.

When both unscheduled and early termination visits exist within the given visit window, the early termination visit will be selected for analysis. When no early termination visits and several unscheduled visits exist, the unscheduled visit closest to the target day will be selected for analysis. If the difference is a tie, the latest unscheduled visit will be selected.

Panel 4: Visit windows

Visit (target day)	Visit window (day is date of assessment minus date of first dose)
Week 2 (Day 14)	Day 8 to 21
Week · (Day 7 · x, where x = 4, 6, 8, …, 16)	Day 7·x-6 to 7·x+7
SFU	36-49 days after last dose

5.2 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 $60 \cdot 60 \cdot 24 \cdot 365.25$. Exposure start date and time and exposure end date and time are defined in Panel 3, Section 5.1.2.

Exposure time will be summarized and listed for the safety analysis set. The summaries will be using descriptive statistics for continuous data as well as number and percentage of subjects with less than 6 weeks of exposure time, 6-11 weeks of exposure time, 12-15 weeks of exposure time, and >= 16 weeks of exposure time.

5.3 Intercurrent events

Two intercurrent events are considered to affect the interpretation of the estimates of the endpoints:

- **Initiation of rescue treatment:** This event occurs when a subject initiates rescue treatment. This event can occur at the discretion of the investigator. The timing of the event is defined as the date of initiation of the rescue treatment recorded in the eCRF.

  Rescue treatment will be defined by the following algorithm: Concomitant medications with ‘Dermatitis atopic’ or ‘Dermatitis infected’ as the preferred term for the indication and either of the following:

  1. ATC2 code H02 or D07.
  2. ATC4 code D11AH.
  3. Preferred name:
     - delgocitinib,
     - crisaborole,
     - methotrexate,
     - ciclosporin,
     - azathioprine,

- mycophenolate-mofetil,
- mycophenolate-sodium,
- mycophenolate-acid,
- ruxolitinib,
- dupilumab,
- upadacitinib or
- abrocitinib

- **Permanent discontinuation of IMP:** This event occurs when a subject is permanently withdrawn from treatment or the trial. This event can occur at the subject's own initiative, at the discretion of the investigator or the sponsor, or if the subject is lost to follow-up.

5.4 Primary endpoints analyses

5.4.1 Definition of endpoints

Two primary endpoints are considered:

- IGA 0/1 at Week 16: obtaining an IGA score of 0 (clear) or 1 (almost clear) at Week 16.

- EASI75 at Week 16: obtaining at least 75% reduction in EASI score at Week 16 relative to baseline.

Both endpoints are binary and take the values ‘1’ (response) and ‘0’ (non-response) depending on whether the condition is met.

5.4.2 Primary analyses

The primary endpoints (IGA 0/1 at Week 16 and EASI75 at Week 16) will be analysed using the composite estimand strategy to handle the occurrence of intercurrent events (initiation of rescue medication or permanent discontinuation of IMP).

Missing data for subjects who do not attend the Week 16 visit and where rescue medication has not been used, nor the subject has permanently discontinued IMP, will be imputed as non-response.

The number and percentage of subjects achieving response will be presented together with the corresponding 95% CI.

The analysis will be based on the FAS.

5.5 Secondary and other endpoints analyses

The secondary endpoint, number of treatment-emergent AEs from baseline up to Week 16, and the analysis of this is covered in Section 5.7.1.

The secondary endpoint, presence of treatment-emergent ADA from baseline to Week 16, and the analysis of this is covered in Section 5.6.

5.5.1 Successful subject self-administration

The subject's ability to self-administer tralokinumab using the autoinjector will be assessed following each administration after baseline (Week 0). The assessment is based on the defined sequence of use steps described in CTP section 11.3 and as outlined in Panel 5.

Successful subject self-administration for administration at trial site or following dosing at home is defined as completion of each defined sequence of use steps without errors. Each step is recorded in the eCRF.

Panel 5 shows the combination of answers that constitutes a successful self-injection. For all other combinations of answers, the self-administration is defined as unsuccessful.

Panel 5: Successful subject self-administration

Question in eCRF	Answer corresponding to errorless completion
Did the subject choose the correct injection area?	Yes*
Did the subject remove the cap?	Yes
Did the subject press device down to begin injection?	Yes
Did the subject hold until the injection is complete?	Yes
Did the yellow plunger cover the viewing window completely when removing the autoinjector from the injection area?	Yes
Was liquid dripping from the tip of the autoinjector when removing it from the injection area?	No

*) The injection area is considered correct if the subject chose left or right anterior thigh, or abdomen.

Abbreviations: eCRF = electronic case report form.

The number and percentage of subjects with successful IMP self-administration when observed in clinic at Week 4 will be presented together with the corresponding 95% CI (based on the Wilson method). Subjects who permanently discontinue IMP before Week 4 and subjects with missing values will be excluded from the analysis.

The analysis will be based on the usability analysis set.

The successful IMP self-administration when administered at home at Week 8, will be analysed in the same way as for the endpoint at Week 4 with the modification that subjects must not have permanently discontinued IMP prior to Week 8.

5.5.2 Other binary efficacy endpoints

Other binary efficacy endpoints are listed in Panel 6. All binary endpoints take the values '1' (response) or '0' (non-response) depending on whether the condition is met.

The binary efficacy endpoints listed in Panel 6, IGA 0/1 and EASI75 will be tabulated from baseline to Week 16 by visit using the same strategy as for the primary endpoints. Missing values where no intercurrent events have occurred, will be imputed as non-response.

Panel 6: Other binary efficacy endpoints

Description of endpoint
EASI90: obtaining at least 90% reduction in EASI score
EASI50: obtaining at least 50% reduction in EASI score
Reduction in Worst Weekly Pruritus NRS/Adolescent's Pruritus NRS of at least 4
Reduction in POEM of at least 4 in adults/ Reduction in POEM of at least 6 in adolescents. Subjects with POEM < 4 for adults / <6 for adolescents at baseline will not be included in the analysis
Reduction in DLQI of at least 4 in adults/Reduction in CDLQI of at least 6 in adolescents. Subjects with DLQI < 4 for adults / CDLQI <6 for adolescents at baseline will not be included in the analysis

5.5.3 Other continuous endpoints and patient reported outcomes

The mean, 95% CI and SD will be calculated for the change and percentage change for other continuous efficacy endpoints listed in Panel 7.

The DLQI will be analysed and presented for adult subjects only, and the CDLQI score will be analysed and presented for adolescent subjects only.

Analysis and data presentation will be based on the FAS.

Panel 7: Other continuous efficacy endpoints

Description of endpoint
Change in Eczema-related Weekly Sleep NRS will be tabulated from baseline to Week 16 by visit.
Change in Worst Weekly Pruritus NRS/Adolescent's Pruritis NRS will be tabulated from baseline to Week 16 by visit
Change in DLQI/CDLQI will be tabulated from baseline to Week 16 by visit.
Change in POEM will be tabulated from baseline to Week 16 by visit. Percentage change in EASI will be tabulated from baseline to Week 16 by visit.

5.6 Pharmacokinetics analysis and antidrug antibodies

5.6.1 Pharmacokinetic analysis

All the PK samples in the trial are trough samples. The trough concentration (C_{trough}) will be listed and descriptive statistics will be applied.

Missing data will not be imputed.

5.6.2 Anti-drug antibodies analysis

Anti-drug antibodies are tabulated as described in the CTP section 14.3.14.

For subjects who develop ADA and are considered treatment boosted or treatment emergent, the IGA score, change in EASI at end of treatment, and titre information will be listed.

Neutralising antibodies (nAb) will be conducted on those serum samples that test positive for ADA. The nAb status will be listed for subjects who develop ADA.

5.7 Safety analysis

The analysis of safety will be presented separately for the treatment period and SFU period.

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

5.7.1 Adverse events

AEs will be coded during the course of the trial according to Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 and presented as described in the CTP section 14.3.12.1.

An AE will be considered treatment emergent if started after the first use of IMP. Only treatment emergent AEs will be summarized and tabulated.

AEs will be presented by preferred terms (PT) and primary system organ class (SOC).

An overall summary of the number (percentage) of AEs, the rate of AEs (number of AEs per 100 patient years of observation time), and the number (percentage) of subjects with any treatment-emergent AEs, death, SAEs, AEs leading to premature discontinuation from IMP and/or withdrawals from the trial, treatment-related AEs, and severe AEs will be presented. In addition, AEs will be presented by severity and causal relationship to IMP.

A summary of all AESIs will be tabulated, and for the AESI injection site reactions, a separate severity grading derived from the data collected according to Panel 9 will be tabulated as described in Section 5.7.2

The number (percentage) of AEs, rate of AEs, and number of subjects with each type of AEs will be tabulated.

SAEs and AESIs will be evaluated separately. A narrative for each SAE will be given.

All AEs recorded during the course of the trial will be included in subject data listings.

5.7.2 Adverse events of special interest

The AEs listed in Panel 8 are considered adverse events of special interest (AESIs) in this trial and will have additional details recorded in the eCRF.

Injection site reactions

Injection site reactions (ISR)s are considered AEs of special interest (AESIs). Additional information on objective signs and subjective symptoms for ISRs, given in Panel 9, will be provided on the AESI form. The information will be used to derive the severity of each sign/symptom according to the severity grading scale given in Panel 10.

Injection site reactions will be summarised descriptively in terms of number of subjects and percentage of subjects reporting an injection site reaction within each category of the injection site reaction severity grading scale given in Panel 10.

Furthermore, all ISRs will be listed in the subject data listings.

Panel 8: Adverse events of special interest

Adverse event of special interest	Additional data to be included in the eCRF (if available)
Injection site reactions	See Panel 9 for details.
Eczema herpeticum	Skin findings: • Lesion type (papules, vesicles, crusts, eroded pits, other). • Disseminated/localised. • Location (face, scalp, back, chest, upper limb, lower limb, genitals). • Present in an area with visible eczema / no visible eczema / present in areas with and without eczema. • Monomorphic/polymorphic. Confirmation of herpes simplex virus (not confirmed, PCR, viral culture, Tzanck, other).
Malignancy diagnosed after treatment assignment, excluding basal cell carcinoma, localised squamous cell carcinoma of the skin, and carcinoma in situ of the cervix	• Histology report available. • Oncology assessment available. • Treatments (surgery, radiation, chemotherapy, other).
Skin infection requiring systemic treatment	• Location (face, scalp, back, chest, upper limb, lower limb, genitals). • Outcome of pathogenic swab (positive, negative, not performed).
Conjunctivitis	• Aetiology (viral, bacterial, allergic, unknown). • Bacterial culture outcome (for events with bacterial aetiology). • Diagnosis confirmed by ophthalmologist.
Keratoconjunctivitis	• Aetiology (infectious, non-infectious, other, unknown). • Bacterial culture outcome (for events with bacterial aetiology). • Diagnosis confirmed by ophthalmologist.
Keratitis	• Aetiology (infectious, non-infectious, other, unknown). • Bacterial culture outcome (for events with bacterial aetiology). • Diagnosis of herpes simplex keratitis (for events with viral aetiology). • Diagnosis confirmed by ophthalmologist.

Abbreviations: eCRF = electronic case report form, PCR=polymerase chain reaction

Panel 9: Adverse events of special interest - injection site reaction

Adverse event of special interest	**Additional data to be collected**	
Injection site reactions	Objective signs	Erythema • Largest diameter (mm) Swelling/Oedema • Largest diameter (mm) • Effect on activity o Does not interfere with activity o Interferes with activity o Prevents daily activity Bruising/Haematoma • Largest diameter (mm) • Effect on activity o Does not interfere with activity o Interferes with activity o Prevents daily activity Induration • Largest diameter (mm) • Effect on activity o Does not interfere with activity o Interferes with activity o Prevents daily activity Other • Description • Largest diameter (mm) • Effect on activity o Does not interfere with activity o Interferes with activity o Prevents daily activity
	Subjective symptoms	Itch • Effect on activity o Does not interfere with activity o Interferes with activity o Prevents daily activity Pain/Burning/Stinging • Effect on activity o Does not interfere with activity o Interferes with activity o Prevents daily activity Other • Description • Effect on activity o Does not interfere with activity o Interferes with activity o Prevents daily activity

Panel 10: Injection site reaction severity grading scale

Injection site reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain	Does not interfere with activity	Interferes with activity	Prevents daily activity
Itching	Does not interfere with activity	Interferes with activity	Prevents daily activity
Erythema	2.5 to 5 cm	5.1 to 10 cm	> 10 cm
Swelling/Oedema	2.5 to 5 cm and does not interfere with activity	5.1 to 10 cm or interferes with activity	> 10 cm or prevents daily activity
Bruising/Hematoma	2.5 to 5 cm and does not interfere with activity	5.1 to 10 cm or interferes with activity	> 10 cm or prevents daily activity
Induration	2.5 to 5 cm and does not interfere with activity	5.1 to 10 cm or interferes with activity	> 10 cm or prevents daily activity

Symptoms assessed and found not present will be graded 0.

5.7.3 Vital signs

Vital signs, observed values and change from baseline, will be summarised at each site visit using mean, standard deviation (SD), median, 1st quartile, 3rd quartile, minimum, and maximum values.

5.7.4 Clinical laboratory evaluation

Laboratory parameters (chemistry and haematology) – observed values and change from baseline – will be summarised at each site visit using mean, SD, median, 1st quartile, 3rd quartile, minimum, and maximum values.

Urinalysis dipstick results and urinalysis investigator interpretation will be listed.

Laboratory parameters (chemistry and haematology), except eosinophils, will be classified as 'low', 'normal', or 'high', depending on whether the value is below, within, or above the reference range, respectively. Eosinophils will be classified at '≤ 0.5', '>0.5 and ≤1.5', or '>1.5'. Three shift tables will be produced; one showing the categories at baseline against those at end of treatment (Week 16), one showing the categories at baseline against the highest post-baseline value, and one showing the categories at baseline against the lowest post-baseline value.

Mean plots with standard deviation (SD) by visit and boxplots of actual values will be presented for the selected laboratory parameters listed below:

- chemistry (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, gamma glutamyl transferase)
- haematology (basophils, eosinophils, leukocytes, lymphocytes, monocytes, neutrophils)

Furthermore, the mean plots with SD by visit will be presented for the change from baseline for the aforementioned selected chemistry and haematology parameters.

5.8 Subgroup analyses

To assess the consistency of the number of responders for the composite estimand across subgroups, the primary endpoints (EASI75 at Week 16 and IGA 0/1 at Week 16) will be analysed by baseline IGA.

Subjects will be divided into two groups depending on their IGA score at baseline; subjects with an IGA score of 3 (Moderate disease) and subjects with an IGA score of 4 (Severe disease), respectively. The subgroup definition will not be changed if group sizes are skewed.

The subgroup analyses will be based on the FAS.

5.9 Interim analysis

An interim analysis including only adult subjects will be made to support submission for marketing approval of tralokinumab. The interim analysis will be based on data collected for adult subjects during the trial period and performed after interim DBL. The interim DBL will be performed when all adult subjects have ended trial participation (i.e., completed the end of trial form). The analyses will be in accordance with those specified in the CTP and in this SAP .

There is no blinding to maintain as this trial is an open label trial, and so there will be no impact on data integrity or trial results from proceeding trial conduct.

6 Changes to analyses described in the protocol

All changes to the specified analyses and derivations planned in the CTP are summarized in Panel 11.

Panel 11: Changes to the analyses described in the protocol

Section in CTP	Description of change	Brief rational
14.2 Trial analysis sets	The description of the full analysis set, and the safety analysis set has been updated such that subjects should both be assigned to treatment and dosed.	The definition in the CTP did not specify subjects to be assigned to treatment, but only dosed.
14.2 Trial analysis sets	In addition to the analysis sets defined in the CTP, an analysis set, called "usability analysis set ", for analysing endpoints related to IMP self-injection has been defined. Furthermore	The analysis set is described in the CTP, but not named. To ease readability and communication it has been defined and named usability analysis set
14.2 Trial analysis sets	A SFU analysis set is added to the list of the analyses sets	To analyse endpoints and assessments related to safety during the SFU period
14.3.16 General principles	In addition to what is stated in the CTP, the lower and upper quartiles will be used to summarise continuous data.	To align outputs with previous trials in the Tralokinumab project.
14.3.16 General principles	Baseline definition is added.	To define the baseline data.
14.3.16 General principles	It has been specified that the Wilson method is used to calculate the confidence interval for the responder analyses, and the statistically method Student's t-CI is used to calculate the CI for the continuous endpoints.	To specify what method is used.
14.3.6 Estimand strategy	Definition of date of permanent discontinuation of IMP has been changed to latest date of early termination visit (if existing) or date of onset of latest AE leading to withdrawal of IMP, otherwise date of the last visit, excluding safety follow-up visit rather than date of last IMP administration.	Definition in the CTP was erroneous.
14.3.3 Exposure and treatment compliance	From exposure start to end, not date of disc. of IMP. Presented both as continuous data and categorical.	End of exposure definition in CTP was erroneous.
14.3.7 Analysis of primary endpoints	Added a subgroup analysis for the primary endpoints (EASI75 at Week 16 and IGA 0/1 at Week 16). Each endpoint will be analysed by baseline IGA.	To look into subgroups.
14.3.4 Rescue medication	Definition of rescue medication has been updated to include upadacitinib and abrocitinib as preferred name.	The two treatments have been approved in the meantime.
14.3.10	Other binary efficacy endpoints will be tabulated from baseline to Week 16 by visit and not only from baseline to week 16 as stated in the protocol.	To assess the efficacy at each visit.
14.3.11	Other continuous efficacy endpoints will be tabulated from baseline to Week 16 by visit and not only from baseline to week 16 as stated in the protocol.	To assess the efficacy at each visit.

14.3.12.1 Adverse events	The percentage of treatment-emergent AEs will not be presented. Rate of AEs (per 100 patient-years of observation time), and percentage of subjects with treatment-emergent AEs will be presented.	Percentage of treatment-emergent AEs was included by mistake in the CTP.
14.3.12.2 Vital Signs	Added reporting of observed values of vital signs.	To align output with previous trial in the Tralokinumab project and the way of data presentation.
14.3.12.3 Clinical laboratory evaluation	Added reporting of observed values of laboratory parameters (chemistry and haematology).	To align output with previous trial in the Tralokinumab project and the way of data presentation.
14.3.12.3 Clinical laboratory evaluation	Added two shift tables for laboratory parameters; one against highest post-baseline value, and one against lowest post-baseline value.	To align output with previous trial in the Tralokinumab project and the way of data presentation.

Abbreviations: AE = adverse event, CTP = clinical trial protocol, EASI = Eczema Area and Severity Index, EASI75 = at least 75% reduction in EASI score from baseline, IGA = Investigator's Global Assessment, IGA 0/1 = IGA score of clear (0) or almost clear (1), IMP = investigational medicinal product.

7 Supporting documentation

7.1 Appendix 1: PRO scoring algorithms

References to the scoring algorithms of the PROs are specified in Panel 12.

Panel 12: PRO scoring algorithms

DLQI	Scored according to: https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/dermatology-life-quality-index
CDLQI	Scored according to: https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/childrens-dermatology-life-quality-index
POEM	Scored according to: https://www.nottingham.ac.uk/research/groups/cebd/documents/methodological-resources/poem-for-self-completion.pdf

8 Change log

Version	Section of SAP	Description of change	Brief rational
2.0	Statistical analysis plan statement	Department names updated for statistical lead and medical lead	Correction of error
	Version history	Date for version 1.0 changed to match date of version 1.0 on front page	Correction of error
	1.2 Trial design	Update of description of DBL for interim analysis and data in scope	To include safety follow up data for all adults in the interim analysis
	5.1 General principles	Removal of description of DBL for interim analysis and data in scope	To include safety follow up data for all adults in the interim analysis
	5.9 Interim analysis	Update of description of DBL for interim analysis and data in scope	To include safety follow up data for all adults in the interim analysis
	6 Changes to analysis described in the protocol	Removal of description for section 14.3.6 about data for interim analysis	This text was removed from section 5.1 General principles as described above
1.0	NA	NA	Original version