Statistical analysis plan

LP0162-1337

Long-term extension trial in subjects with atopic dermatitis who participated in previous tralokinumab trials – ECZTEND

Design of trial:

Phase 3 – long-term extension trial

An open-label, single-arm, multi-centre, long-term extension trial to evaluate the safety and efficacy of tralokinumab in subjects with atopic dermatitis who participated in previous tralokinumab clinical trials

LEO Pharma A/S	**Trial ID:**	**LP0162-1337**
	Date:	**19-Jul-2024**
	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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PPD Biostatistics

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

AD	atopic dermatitis
ADA	anti-drug antibodies
ADR	adverse drug reaction
ADRG	analysis data reviewer's guide
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
CTP	clinical trial protocol
CTR	clinical trial report
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI50/75	at last 50/75% reduction in EASI from baseline (in the parent trial)
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL 5-Dimension Health Questionnaire 5-Level
FAS	full analysis set
HDL	high density lipoprotein
HLT	MedDRA high level term
hMI	hypothetical multiple imputation of missing data and any unobserved data
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator's Global Assessment
IGA 0/1	IGA score of 0 (clear) or 1 (almost clear)
IMP	investigations medicinal product
LDL	low density lipoprotein
LOCF	last observation carried forward
LoE	loss of efficacy
MedDRA	Medical Dictionary for Regulatory Activities

MI	multiple imputation
mNRI-MI-Hyp	modified non-responder imputation with multiple imputation of missing and any unobserved data with treatment adherence multiple imputation strategy
NRI	non-responder imputation
NRS	numerical rating scale
PCS	potentially clinically significant
PK	pharmacokinetic
PMDA	Japan Pharmaceuticals and Medical Devices Agency
POEM	Patient-Oriented Eczema Measure
PT	preferred term
Q2W	every 2 weeks
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SCORAD	Scoring Atopic Dermatitis
SD	standard deviation
SFU	safety follow-up
SOC	system organ class
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event

Version history

The SAP for trial LP0162-1337 is based on the CTP version 14.0 dated 21-Feb-2022.

SAP version	Date	Change	Rationale
1.0		Not applicable	Original version

1 Introduction

The statistical analysis will be performed as outlined in the CTP version 14.0. 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 CTP-planned analyses are described in Section 6.

1.1 Trial objectives and endpoints

Panel 1: Trial objectives and endpoints

Objectives	Endpoints
Primary objective	Primary endpoint
To evaluate the long-term safety of tralokinumab	• Number of adverse events during the treatment period from baseline up to Week 268
Secondary objectives	Secondary endpoints
To evaluate the efficacy of tralokinumab given as continuous treatment, re-treatment, or introduced for the first time in tralokinumab-naïve subjects	• IGA score of 0 (clear) or 1 (almost clear) at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248 • EASI75[1] at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248
	Other endpoints
	• Change in EASI score from baseline[2] to Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248 • Change in SCORAD from baseline[2] to Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248 • Change in POEM score from baseline[2,3] to Weeks 16, 56, 80-88, 104, 128-136, 152, 184, 216, and 248 • Change in DLQI score from baseline[2,3] to Weeks 16, 56, 80-88, 104, 128-136, 152, 184, 216, and 248 in adult subjects[7] • Change in CDLQI[4] score from baseline[2,3] to Weeks 16, 56, 80-88, 104, 128-136, 152, 184, 216, and 248 in adolescent subjects[6] • Change in EQ-5D-5L score from baseline[2,3,5] to Weeks 16, 56, 80-88, 104, 128-136, 152, 184, 216, and 248 • Presence of anti-drug antibodies (yes/no) • Time from first dose to permanent discontinuation of tralokinumab

	• Proportion of time with EASI75[1] after first occurrence of EASI75 during treatment period in ECZTEND • Proportion of time with EASI50[1] after first occurrence of EASI50 during treatment period in ECZTEND • Proportion of time with IGA 0/1 after first occurrence of IGA 0/1 during treatment period in ECZTEND • Worst Weekly Pruritus NRS at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248 in adult subjects[7] • Worst Weekly Pruritus NRS at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248 in adolescent subjects[6] • Eczema-related Weekly Sleep NRS at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248 in adult subjects[7] • Eczema-related Weekly Sleep NRS at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248 in adolescent subjects[6] • Use of topical treatment during the last week at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248

Notes:

[1] EASI75 and EASI50 will be calculated based on baseline EASI score in parent trial. The endpoint is not applicable for subjects from the parent trial TRA-WEI-0015-I, as data from the parent trial will not be transferred to LEO Pharma.

[2] 'Change from baseline' is defined as change from baseline in the parent trial. Endpoints are not applicable for subjects from the parent trial TRA-WEI-0015-I, as data from the parent trial will not be transferred to LEO Pharma.

[3] Endpoint is not applicable for subjects from the parent trial LP0162-1342, as these subjects did not have POEM, DLQI/CDLQI, or EQ-5D-5L assessments in the parent trial and thus are missing baseline assessments.

[4] All subjects from the parent trial LP0162-1334, independent of the subject's age during participation in ECZTEND, performed the CDLQI, an adolescent's pruritis NRS with a recall period of past 7 days, and an eczema-related sleep NRS with a recall period over the past 7 nights.

[5] Endpoint is not applicable for subjects from the parent trials LP0162-1334 and -1343, as these subjects did not have EQ-5D-5L assessments in the parent trial and thus are missing the baseline assessment.

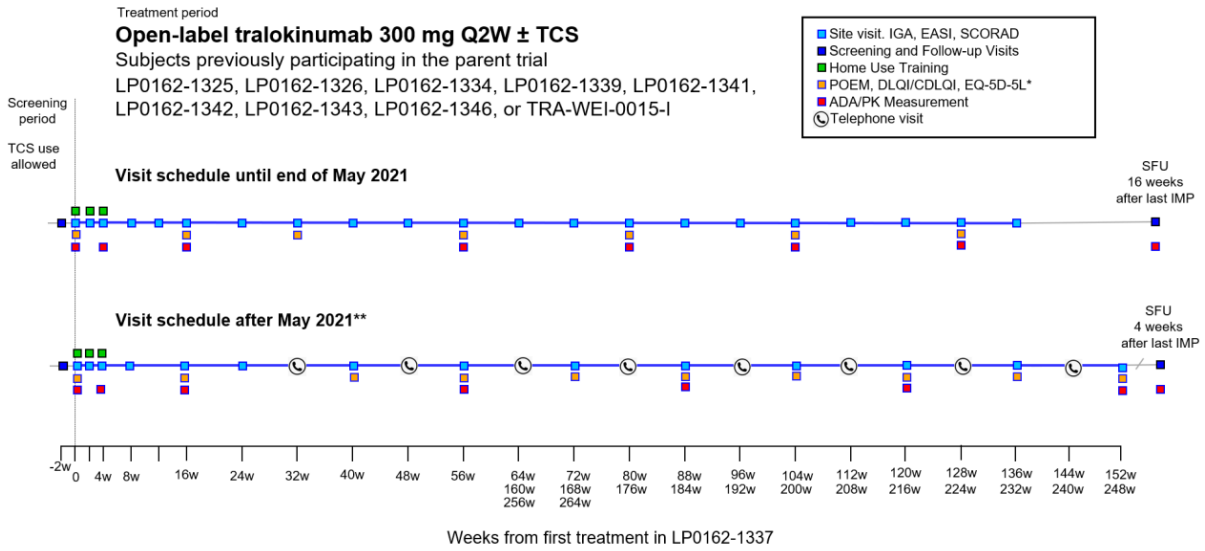
[6] Adolescent subjects are defined as subjects from the LP0162-1334 trial, regardless of their age during participation in ECZTEND.

[7] Adult subjects are defined as subjects not from the LP0162-1334 trial, regardless of their age during participation in ECZTEND.

Abbreviations: CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI75/EASI50 = at least 75%/50% reduction in EASI score, relative to baseline in parent trial; EQ-5D-5L = EuroQoL 5-Dimension Health Questionnaire 5-Level; IGA = Investigator's Global Assessment; NRS = numeric rating scale; POEM = Patient-Oriented Eczema Measure; SCORAD = Scoring Atopic Dermatitis.

1.2 Trial design

Panel 2: Trial design



Notes: Subjects were included in ECZTEND after completion of the treatment period in the parent trial, and continued with a long-term treatment period of approximately 0.5 to 5 years in ECZTEND. Subjects who did NOT re-consent to participation in the trial after May 2021 stopped IMP treatment by end of May 2021 followed by 16 weeks of SFU (top row visit schedule). * Subjects from the parent trial LP0162-1334 did not perform the EQ-5D-5L. ** Visit schedule after May 2021 applied to subjects who consented to continue in the trial after May 2021, or who were included in the trial after May 2021. Treatment ended at a country-specific treatment end date, or by end of May 2022 (subjects from the parent trial LP0162-1334).

Abbreviations: ADA = anti-drug antibodies; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EQ-5D-5L = EuroQoL 5 Dimension Health Questionnaire 5-Level; IGA = Investigator's Global Assessment; IMP = investigational medicinal product; PK = pharmacokinetics; POEM = Patient Oriented Eczema Measure; Q2W = every second week; SCORAD = Scoring Atopic Dermatitis; SFU = safety follow-up; TCS = topical corticosteroids; w = weeks.

Protocol amendments

The following CTP amendments significantly affected data interpretation, analyzed populations, or statistical analyses:

- Amendment 2 (31-Aug-2018):
  - Allowed subjects from parent trial LP0162-1346 to enter ECZTEND.
  - Changed the timeframe of the primary endpoint from "up to Week 128" to "last treatment visit".

- Amendment 6 (17-Feb-2020):
  - Changed the timeframe of the primary endpoint from “last treatment visit” to “up to Week 142”.
  - Allowed adolescent subjects from parent trial LP0162-1334 to enter ECZTEND including associated assessments and precautions.
  - Increased estimated sample size to 1500 subjects.

- Amendment 7 (25-Nov-2020):
  - Updated the visit schedule after May 2021, extending the trial up to 5 years.
  - Converted every other site visit after Week 24 to telephone visits.
  - Allowed subjects from parent trial LP0162-1343 and TRA-WEI-0015-I to enter ECZTEND.
  - Added country specific end of treatment dates.
  - Updates to all endpoints in accordance with the extension of the trial and update to the schedule of assessments.

For a complete overview of all changes introduced in protocol amendments, see the CTP Appendix 8.

2 Testing strategy

No testing has been specified.

3 Sample size

Sample size documentation is provided in the CTP Section 14.1.

4 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All subjects receiving tralokinumab will be included in the FAS and will be analysed for efficacy. 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 tralokinumab from the FAS, a justification addressing ICH E9 will be given.

The SAF will be identical to the FAS, as all subjects receiving tralokinumab will be included in the SAF. However, subjects decided to be excluded from the FAS will not also be excluded in the SAF. Any exclusions from the SAF will be justified separately addressing ICH E9.

All subjects receiving tralokinumab and starting in the safety follow-up will be included in a safety follow-up analysis set. Any exclusions will be identical to the safety analysis set.

Data from the investigator-initiated parent trial TRA-WEI-0015-I will not be transferred to LEO Pharma. Thus, endpoints defined as change from baseline (in the parent trial) will not be calculated for subjects from this trial, and data from this trial will not be included in tables summarising endpoints defined as change from baseline or where data are presented by responder/non-responder status. Subjects from TRA-WEI-0015-I will be contributing to the primary endpoint and included in summary tables where possible.

The decisions regarding inclusion/exclusion of subjects or subject data from the trial analysis sets will be documented in the Classification Brief.

5 Statistical analysis

All presentations of data will be made for the total ECZTEND population with above analysis sets applied as appropriate.

5.1 General principles

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 observed data will be summarised using the number and percentage of subjects in each category and, if applicable, by tralokinumab naïve, re-treated, and continuously treated, and by washed-out subjects.

Continuous observed data will be summarised using the mean, SD, median, 1st quartile, 3rd quartile, minimum, and maximum values and, if applicable, by tralokinumab naïve, re-treated, and continuously treated, and by washed-out subjects.

Tralokinumab treatment naïve, re-treated, and continuously treated, and washed-out subgroups have been defined in Section 7.1.

All endpoints derived using baseline values are derived using the parent trial baseline value unless otherwise indicated.

For analyses using multiple imputation, the seed number used will be 32 and 100 MI will be carried out.

If region is used as a covariate or sub-group variable, it will be defined with the levels: North America, Europe, and Asia.

5.2 Intercurrent events

The following intercurrent events are defined to describe the treatment effect that is targeted with the different estimand strategies described underneath.

- **Treatment completion:** This intercurrent event occurs either when a subject completes the period of the trial the subject consented to or is withdrawn from the trial due to tralokinumab becoming commercially available in their country. This intercurrent event is introduced mainly due to the extension amendment introduced in May 2021. Notably, it was not collected in the eCRF whether a subject withdrew due to not consenting to continue in the extension of the trial. Subsequently, an algorithm was built such that withdrawals close (17 days) to the country-specific closure date were classified as treatment completers instead of as having permanently discontinued IMP. See the ADRG for a complete algorithm defining treatment completion.

- **Permanent discontinuation of IMP:** This intercurrent event occurs when a subject is withdrawn from trial while under treatment. It can occur at the subjects' own initiative, at the discretion of the investigator or the sponsor, or if the subject is lost to follow-up:
    - **Due to lack of efficacy (LoE) or adverse event (AE):** This intercurrent event occurs when it is specified that the primary reason for withdrawal from trial while under treatment is due to either LoE, or AE. Of note, the reasons "withdrawal by subject", "lost to follow-up" and "other" were queried to ensure that the underlying reason was not LoE or AE.
    - **Not due to LoE nor AE:** the complement to the previously specified reasons.

5.3 Baseline presentations

Due to safety-related analyses specified for subjects coming from the LP0162-1334 trial in the protocol, baseline presentations will be specified where applicable for subjects from the LP0162-1334 trial.

5.3.1 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics (e.g. efficacy variables at parent trial baseline and ECZTEND baseline [age, sex, ethnicity, race]) and the latest treatment regimen in the parent trial (placebo, tralokinumab, tralokinumab + TCS) will be presented for the SAF and by tralokinumab-naïve/re-treated/continuously treated subjects in the SAF. For the re-treated and continuously treated subjects, the presentation will further

be divided by responder/non-responder status in the parent trial; clinical response is defined as achievement of IGA 0/1 or EASI75 at the last assessment in the parent trial.

In addition, due to variable country closures due to by the commercialization of tralokinumab, the above defined descriptive statistics will be made for those subjects still ongoing in trial (i.e. those who have neither withdrawn nor completed the trial) at weeks 56, 104, 152, 216, and 264 relative to ECZTEND baseline for the SAF.

The above will also be made for subjects transferring in from LP0162-1334. However, only presenting summaries of the total, tralokinumab naïve, re-treated, and continuously treated, not the washed-out subjects.

5.3.2 Medical, Skin, and Atopic disease histories

Medical, skin, and atopic disease histories will be presented for the SAF.

The above will also be made for subjects transferring in from LP0162-1334. However, only presenting summaries of the total, tralokinumab naïve, re-treated, and continuously treated, not the washed-out subjects.

5.4 Disposition of subjects, medication, procedures, and exposure

5.4.1 Disposition of subjects

The reasons for withdrawal from the trial will be presented for the SAF, using the Aalen-Johansen cumulative incidence function estimator, over both the treatment period and the safety follow-up period.

In addition, reasons for withdrawal from the trial and reasons for permanent discontinuation of IMP will also be presented in the same manner over the treatment period for the SAF.

A stacked bar plot will be made showing the proportion of subjects in each region ongoing in the trial (i.e. those who have neither withdrawn nor completed the trial) over the treatment period and the safety follow-up period for the SAF.

The above will also be made for subjects transferring in from LP0162-1334. However, only presenting summaries of the total, tralokinumab naïve, re-treated, and continuously treated, not the washed-out subjects.

5.4.2 Concomitant medication and concurrent procedures

Concomitant medication at ECZTEND baseline will be presented for the SAF.

Concomitant medication in the treatment period will be presented for the SAF.

All concomitant medications and concurrent procedures will be listed.

The above will also be made for subjects transferring in from LP0162-1334. However, only presenting summaries of the total, tralokinumab naïve, re-treated, and continuously treated, not the washed-out subjects.

5.4.3 Extent of exposure and treatment compliance

Exposure

Exposure to treatment will be presented for the SAF as days of exposure in total, by exposure time cutoffs, and by parent trial.

Days of exposure will be calculated as the number of days from the date of the first IMP dose in ECZTEND to the date of the end of treatment visit, or – if the end of treatment visit is missing – to the date of permanent discontinuation of IMP.

Treatment compliance

Adherence will be presented for the SAF.

The above will also be made for subjects transferring in from LP0162-1334. However, only presenting summaries of the total, tralokinumab naïve, re-treated, and continuously treated, not the washed-out subjects.

5.5 Primary analysis

The primary endpoint in this trial is the number of adverse events during the treatment period from baseline up to Week 268, and the analysis of this endpoint is covered in the safety analysis section.

5.6 Efficacy analysis

All efficacy endpoints will be analysed using the FAS. In addition, to support the secondary objective of the trial, all efficacy analyses will be done by tralokinumab-naïve, re-treated, and continuously treated, and in addition for the washed-out subgroup (Section 7.1).

5.6.1 Analysis of Secondary endpoints

For definitions of endpoints see Panel 1.

5.6.1.1 Binary endpoints

5.6.1.1.1 Primary analysis

Observed cases analysis by each scheduled visit will be performed, presenting proportions with a 95% Wilson CIs.

Figures will be made of the observed proportions of responders by visit with CI and a table appended showing the number of subjects with observed data and number of subjects who have not dropped out at each visit.

5.6.1.1.2 Sensitivity analyses

The strategies used in these sensitivity analyses use hypothetical assumptions to investigate potential survival bias and do not necessarily represent the truth if all subjects had continued. The goal is to provide multiple hypothetical scenarios, of which some will reflect extreme assumptions and some will be closer to the expected true estimate. Examining both extreme and realistic hypothetical scenarios should allow for a reasonable discussion of where the true estimate is.

All analyses will be presented by all planned assessments with 95% Wilson CIs, and where data is being multiply imputed, Rubin's rule will be applied using Lott and Reiter's formula for Wilson CIs with MI (1).

5.6.1.1.2.1 Hypothetical MI of missing data and any unobserved data (hMI)

This sensitivity analysis seeks to mitigate possible survival bias by estimating the response if all subjects had continued in the trial like they were before they dropped out.

The proportion of responders will be calculated by each scheduled visit based on both observed, and multiply imputed missing or unobserved assessment data. The missing assessment data will be imputed using a 2-step MI strategy involving both a regression-based approach imputing data up to the 1st year (Week 56 visit) in the trial and a within-subject approach imputing data after the 1st year in the trial. For the complete technical definition of the 2-step MI strategy please see section 5.6.1.1.2.3. The split at 1 year was chosen for several reasons:

1. Subjects will enter the trial differently, some being untreated or washed-out of tralokinumab and others may be under continuous treatment with tralokinumab when starting the trial. A visit-sequential full conditional specification regression-based approach is ideal to reflect this expected change over time in the overall proportion of response.

2. Survival bias affecting the proportion of responders can within reason be mitigated/minimized provided suitable adjustment in the 1st year. This is because a sizable part and broadly defined population were followed-up without interruptions during the first year.
3. After 1 year, the population can be assumed to have regressed to its mean while under continuous treatment with tralokinumab.

This hypothetical assumption applied to the imputation of missing data from subjects who either completed treatment (e.g. due to commercialization of tralokinumab in their country) or permanently discontinued IMP is strong. However, assuming that these subjects continued as if they had regressed to their within-subject mean is appropriate under this hypothetical sensitivity scenario as it attempts to estimate the proportion of responders under minimal influence of survival bias.

5.6.1.1.2.2 mNRI-MI with treatment adherence MI strategy (mNRI-MI-Hyp)

This sensitivity analysis seeks to estimate a lower bound of the response by estimating the response achieved without permanent discontinuation of IMP due to LoE or AE if all subjects who withdrew for other reasons had continued in the trial like they were before they dropped out.

The response at each scheduled visit will be calculated based on both observed and multiply imputed missing or unobserved assessment data, with those having permanently discontinue IMP due to LoE or AE prior to the analysed visit imputed as non-responders. Missing assessment data will be imputed using the same 2-step MI strategy (see section 5.6.1.1.2.3) as in the hMI sensitivity analysis. Permanent discontinuations of IMP due to LoE or AE of subjects who permanently discontinued IMP for other reasons or completed the trial will be imputed using the hypothetical treatment adherence MI strategy (see section 5.6.1.1.2.3) onto subjects who either completed treatment or permanently discontinued IMP for other reasons than LoE or AE after the time they discontinue.

This hypothetical scenario sets out to estimate a lower bound of efficacy by assuming that subjects who are either observed or imputed to permanently discontinue of IMP due to LoE or AE are perpetually considered non-responders. In dealing with subjects who drop-out early, it sets a strong assumption that regression-to-the-mean can be assumed when imputing assessment data. But in doing so, this sensitivity strategy targets the same underlying target of estimation established in trials of other similar drugs in AD long-term extension trials (2) where subjects have been non-responder imputed based only on observed permanent discontinuation of IMP due to LoE or AE, with assessment data imputed using last

observation carried forward. However, last observation carried forward will not be used as it is not appropriate, see e.g., “Fallacies of Last Observation Carried Forward” (3).

5.6.1.1.2.3 Imputation strategies

2-step MI strategy

A 2-step MI strategy will be employed to mitigate potential survival bias as reasoned above. MI of missing data and data unobserved after intercurrent events can be used by the different sensitivity analyses per the need of the various estimation requirements:

1. Data up until the Week 56 visit will be imputed using a Full Conditional Specification gaussian regression-based MI model adjusting for previous visit (if planned visit exist), next visit (if planned visit exist), parent trial, and region. If the score being imputed is ordinal or binary, an ordinal logistic regression model will be used instead. The assumption here is that the data used in the MI regression model are robust enough.
2. Data after the Week 56 visit will be imputed using a within-subject non-parametric approach leveraging the proportion of response each subject has achieved estimated using linear interpolation across observed and (in the previous step) imputed scores. This proportion of response could also be called a within-subject AUC of days in response. The imputation will be derived in the following 3 steps:
    1. All days between observed and imputed visits will be imputed on the assessment’s scale by using linear interpolation between visits. For binary and ordinal scores, the imputed value will be rounded.
    2. Then all days will be transformed into the binary endpoint and an average of those 1s (response) and 0s (non-response) going one year back (but not further back than the Week 16 visit) will be the AUC of days in response.
    This assumes that from the Week 16 visit that all subjects have regressed to their individual mean while under long-term treatment with tralokinumab (due to the safety follow-up between parent trials and ECZTEND with no dosing).
    3. An imputed response at each day, including planned visits, after the intercurrent event will then be drawn from the Bernoulli distribution by using the AUC of days in response as a probability.

Hypothetical treatment adherence MI strategy (Hyp**)**

MI of treatment adherence status at end of the treatment period, t_{EoTrt}, for subjects experiencing an intercurrent event, at time t_{ICE}, will be imputed based on the semi-parametric Cox proportional hazard model. The model will provide an estimated probability $\hat{p}(t_{\text{EoTrt}}$, region, parent trial) of being on treatment at the later time t_{EoTrt} conditional on being on

treatment at the earlier time t_{ICE} in the hypothetical scenario where permanent discontinuation of IMP due to pandemic restrictions would not occur. The conditional probability $\hat{p}$ will be calculated as the estimated survival function evaluated at t_{EoTrt} divided by the same function evaluated at time t_{ICE} (with $t_{ICE} < t_{EoTrt}$) and imputed using random draws from an exponential distribution with rate $\hat{p}$. For specific regional analyses, t_{EoTrt} may vary depending on the scarcity of data at the end the treatment period, but for summaries of the main populations Week 264 will be used.

5.6.1.1.3 Supplemental analysis

To evaluate the efficacy of tralokinumab given as continuous treatment, re-treatment, or introduced for the first time in tralokinumab-naïve subjects, each specified analysis above will also be done within each of the tralokinumab naïve, re-treated, continuously treated, and washed-out sub-populations.

5.6.2 Analysis of other endpoints

Due to the changed visit structure introduced in May 2021, some endpoints have been specified as combining data from 2 possible visits, e.g., Change in DLQI/CDLQI score from baseline to Weeks 80-88. The rule for handling these endpoints will be to calculate the endpoint based on the first existing data. Hence, where a subject had an assessment at both Week 80 and Week 88, the Week 80 assessment (corresponding to approximately 1½ years) will be prioritised for the Week 80-88 endpoint evaluation. Likewise, the Week 128 assessment (~ 2½ years) will be prioritised for the Week 128-136 endpoint evaluation.

The DLQI score will be presented for subjects from the parent trials LP0162-1325, -1326, -1339, -1341, -1343, and -1346. The CDLQI score will be presented for subjects from the parent trial LP0162-1334. As subjects from the parent trial LP0162-1342 did not have POEM, DLQI, or EQ-5D-5L assessments in the parent trial, the change from baseline is not applicable. As subjects from the parent trials LP0162-1334 and -1343 did not have EQ-5D-5L assessments in the parent trial, the change from baseline is not applicable. Changes from baseline will not be presented for subjects from the parent trial TRA-WEI-0015-I since data from this investigator-initiated trial have not been transferred to LEO Pharma (see the CTP Section 14.2).

5.6.2.1 Continuous endpoints

5.6.2.1.1 Primary analysis

As observed according to general principles.

Figures will be made with the median and 1st and 3rd quartiles and an table appended showing the number of subjects with observed data at each visit.

5.6.2.1.2 Sensitivity analysis

No sensitivity analysis will be made for continuous other endpoints.

5.6.2.1.3 Supplemental analysis

To evaluate the efficacy of tralokinumab given as continuous treatment, re-treatment, or introduced for the first time in tralokinumab-naïve subjects, each specified analysis above will also be done by tralokinumab naïve, re-treated, continuously treated, and washed-out sub-populations.

5.6.2.2 Proportion of response over time endpoints

5.6.2.2.1 Primary analysis

The proportion of response over time will be estimated by the AUC over daily responses estimated through linear interpolation between observed assessments made at scheduled visits. The analysis will calculate the mean proportion (assumed continuous) and 95% Wald CI appended, with the standard deviation, median, 1st and 3rd quartiles, and minimum and maximum values appended as well.

5.6.2.2.2 Sensitivity analysis/analyses

No sensitivity analyses have been defined.

5.6.2.2.3 Supplemental analyses

A supplementary analysis will be appended for the primary analysis, where each estimated percentage of days in response will be used to analyse the endpoint rephrased in to “subjects with ≥x% of days in response” where x is defined as the whole numbers 0, 1, 2, …,100. The subsequent proportion of subjects with ≥x% of days in response will be estimated with 95% Wilson CIs.

The second supplementary analysis, will be re-made for the primary and the above supplemental analysis over the following periods: Week 0-<16, Week 16-<104, Week 104-<200, and Week 200-264, in addition to the overall treatment period.

5.7 Pharmacokinetics analysis

The pharmacokinetics analysis is tabulated as described in the CTP Section 14.3.9.

5.8 Safety analysis

Safety endpoints will be analysed using the SAF.

5.8.1 Adverse events

AEs will be coded during the course of the trial according to MedDRA version 20.0 but analysed in MedDRA version 27.0.

Only TEAEs will be summarized in this trial. AEs were considered treatment emergent if they started after first dose of IMP or started before first dose of IMP and worsened in severity after first dose of IMP. All AEs recorded during the trial will be listed.

For the treatment and SFU periods, presentations of AEs by SOC and PT will include summaries of the following categories of AEs:

- All AEs.
- Frequent AEs (≥5% of subjects reporting the AE in the total population).
- Frequent AEs (occurring with an incidence rate ≥ 2.5 in the total population).
- SAEs.
- AEs leading to withdrawal from the trial.
- Probably or possibly related AEs.
- Severity of AEs (mild, moderate, and severe AEs presented separately).

Summaries will include the percentage and number of subjects with an AE, number of AEs, patient-years of exposure up until the first event, incidence rate of AEs (rate of new events/occurrences, calculated as the number of subjects with an AE per 100 patient-years of exposure at risk defined as patient-years up until the first event or end of exposure [whichever came first]), and occurrence rate of AEs (rate of events/occurrences calculated as the number of AEs per 100 patient-years of exposure up until end of exposure).

Overviews of AEs will be appended for the above-mentioned categories of AEs and will include the following information: SAEs, severity (mild, moderate, or severe), relationship to IMP (probably, possibly, and not related), AEs probably or possibly related to IMP, AEs leading to withdrawal from trial and/or permanent discontinuation of IMP, outcome, and action taken with IMP.

For the SFU period, all AEs and SAEs will be presented by an overview summary and by SOC and PT using the safety follow-up analysis set.

The above summaries will also be made separately for subjects who transferred from the parent trial LP0162-1334. Secondly, as the frequency of site visits is reduced after May 2021, 2 additional overall AE summary tables will be presented, one will exclude events and exposure time after May 2021 and the second will only include events and exposure time after May 2021. Thirdly, the data will be presented by tralokinumab naïve, re-treated, and continuously treated, and by washed-out subjects using the above defined summaries.

5.8.1.1 ECZTEND defined adverse events of special interest (ECZTEND-AESI)

ECZTEND-AESIs will be presented overall within each AESI, and by SOC and PT, as defined for TEAEs. Additionally collected information for each of the defined ECZTEND-AESIs will be summarised. For their definition see Panel 6.

Panel 3: AESIs (as defined in the CTP)

AESIs	Reason for inclusion
Eczema herpeticum	Eczema herpeticum is a well-known severe skin infection in patients with AD. Eczema herpeticum occurs in lesioned AD skin – the additional information collected can be used to adjudicate the events, if needed.
Malignancy diagnosed after treatment assignment, excluding basal cell carcinoma, localised squamous cell carcinoma of the skin, and carcinoma in situ of the cervix	There has been no indication of a higher risk of malignancy with tralokinumab treatment compared with placebo. However, as is typical for immunomodulating biologics, malignancy is considered an important potential risk for tralokinumab.
Skin infections requiring systemic treatment	The skin barrier is expected to improve during treatment with tralokinumab. Additional information is collected to better describe location and pathogen.
Conjunctivitis**	Important potential risk in the tralokinumab risk management plan. Due to focus on eye disorders.
Keratoconjunctivitis**	Due to focus on eye disorders.
Keratitis**	Due to focus on eye disorders.

**: grouped in AESI ‘Eye disorders’

5.8.1.2 Adverse drug reactions

These ADRs of tralokinumab (as of writing this SAP) will be presented in the same way as for the AESIs. The ADRs of tralokinumab are defined in Panel 7.

5.8.2 Vital signs

Vital signs will be tabulated as described in the CTP Section 14.3.8.2. However, only presenting summaries of the total, tralokinumab naïve, re-treated, and continuously treated, not the washed-out subjects.

Additionally, vital sign values will be considered potentially clinically significant if satisfying the PCS criteria specified in the ADRG. All post-baseline measurements (including samples from unscheduled visits) will be included in the search for PCS values. Number and percentage of subjects with at least one post-baseline PCS value will be summarised with the denominator being all subjects with at least one post-baseline assessment. All PCS values will be included in the listings.

5.8.3 Physical examination

Physical examinations reported as 'abnormal, clinical significant' will be listed.

5.8.4 Clinical laboratory evaluation

Clinical laboratory evaluations will be tabulated as described in the CTP Section 14.3.8.3. However, only presenting summaries of the total, tralokinumab naïve, re-treated, and continuously treated, not the washed-out subjects.

Additionally, shift tables will be produced for relevant laboratory tests showing categories at baseline against highest or lowest test measurement in the treatment period (see Panel 4).

Panel 4: Clinical laboratory test where shift tables will be prepared for lowest/highest measurement in the treatment period

Clinical laboratory test	Shift table to lowest	Shift table to highest
Chemistry		
Sodium	Yes	Yes
Potassium	Yes	Yes
Creatinine	-	Yes
Calcium	Yes	Yes
Alkaline phosphatase	-	Yes
Aspartate aminotransferase	-	Yes
Alanine aminotransferase	-	Yes
Bilirubin	-	Yes
Cholesterol	-	Yes
LDL cholesterol	-	Yes
HDL cholesterol	Yes	Yes

Clinical laboratory test	Shift table to lowest	Shift table to highest
Triglycerides	-	Yes
Glucose (non-fasting)	Yes	Yes
Hematology		
Hemoglobin	Yes	Yes
Neutrophils, segmented	Yes	-
Lymphocytes	Yes	Yes
Monocytes	Yes	Yes
Eosinophils	-	Yes
Basophils	-	Yes
Platelets	Yes	Yes

Abbreviations: HDL = high density lipoprotein; LDL = low density lipoprotein; - = not applicable.

Laboratory values will be considered potentially clinically significant if satisfying the PCS criteria specified in the ADRG. All post-baseline measurements (including samples from unscheduled visits) will be included in the search for PCS values. For haematology and chemistry laboratory parameters, the number and percentage of subjects with at least one post-baseline PCS value will be summarised with the denominator being all subjects with at least one post-baseline assessment. All PCS values will be included in the listings.

Subjects fulfilling Hy's law will be presented.

5.8.5 ECG

The overall central evaluation of ECGs will be summarised and listed. The overall central evaluation of ECG data will be presented using shift tables. However, only presenting summaries of the total, tralokinumab naïve, re-treated, and continuously treated, not the washed-out subjects.

All other ECG parameters collected will be listed.

5.8.6 Anti-drug antibodies

The ADA status categories are updated compared to the CTP Section 14.3.8.4 to incorporate ADA data from the parent trial.

The ADA status will be categorized as below, where all ADA assessments from the parent trial and ECZTEND are taken into account. For subjects who received tralokinumab treatment in the parent trial, 'first tralokinumab dose' refers to the first tralokinumab dose in the parent trial, if applicable.

The ADA status will be categorised as follows:

ADA positive

- Pre-existing: At least 1 positive ADA assessment before first tralokinumab dose, no post-tralokinumab ADA response greater or equal to 4-fold over the maximum pre-tralokinumab titre level. At least 1 positive post-tralokinumab ADA assessment.
- Treatment-boosted: At least 1 positive ADA assessment before first tralokinumab dose, at least 1 post-tralokinumab ADA response greater or equal to 4-fold over the maximum pre-tralokinumab titre level.
- Treatment-emergent: All ADA assessments negative or missing before first tralokinumab dose, at least 1 positive ADA response after first tralokinumab dose.
    - Persistent: Positive ADA for at least 2 consecutive visits at least 10 weeks apart.
    - Indeterminate: Only the last ADA response positive.
    - Transient: Neither persistent nor indeterminate.

ADA negative

- All ADA assessments negative or missing. At least one non-missing ADA assessment after first tralokinumab dose.

Perishing ADA

- At least 1 positive ADA assessment before first tralokinumab dose, all ADA assessments negative after first tralokinumab dose.

No post-baseline

- No ADA assessments after first tralokinumab dose.

For subjects with an ADA positive measurement during the trial, the development in EASI and neutralising antibodies (nAB) will be presented graphically and listed (IGA included).

Presentations will only present the total, tralokinumab naïve, re-treated, and continuously treated, not the washed-out subjects.

5.9 Interim analysis

At the time of writing this SAP several analyses have been conducted. Mainly, an interim report was prepared for EMA which delivered a comprehensive analysis focused solely on safety analyses. Japanese subjects in ECZTEND have been analysed for submission to PMDA. Several abstracts, posters, oral presentations, and articles have been presented and/or published featuring analyses from ECZTEND both in terms of safety and efficacy analyses on differing data-cuts.

6 Changes to analyses described in the protocol

Panel 5 summarises the changes to the analyses planned in the protocol.

Panel 5: Changes to the analyses described in the CTP

Section in the CTP	Description of change	Brief rational3
14.3.5	The specified strict NRI sensitivity analysis has been replaced by 2 sensitivity analyses.	The specified sensitivity analysis was not reasonable as it was not possible to distinguish causes based on the original intent, and due to the amendment extending the trial causing some subjects to not consent to continuing in the trial. A modified NRI method has been introduced as a replacement together with appropriate MI method.
14.3.5	No split on response vs non-response based on the last assessment in parent trials.	The last assessment is not necessarily representable of a fluctuating disease like AD and is conditioned by a lot of other factors, e.g. differing parent trial treatment periods and procedures.

Abbreviations: AD = atopic dermatitis; CTP = clinical trial protocol; MI = multiple imputation; NRI = non-responder imputation.

7 Supporting documentation

7.1 Tralokinumab naïve, re-treated, continuously treated, and washed-out subjects

For summary tables grouped by tralokinumab naïve, re-treated, continuously treated subjects the grouping is based on the following principle:

- *Tralokinumab naïve* subjects have not received any planned tralokinumab treatment in parent trial.
- *Continuously treated* subjects have had a period shorter than 16 weeks (5 half-lives of tralokinumab) between last tralokinumab administration in parent trial and first tralokinumab administration in ECZTEND.
- R*e-treated* subjects have had a period of 16 weeks or longer between last tralokinumab administration in parent trial and first tralokinumab administration in ECZTEND. Thus, full washout between treatment in ECZTEND and parent trial.

The combined group of tralokinumab naïve and re-treated subjects, which consists of those new to tralokinumab or washed out from tralokinumab will be called ‘washed-out subjects’.

As data from the TRA-WEI-0015-I study have not been transferred to this study, subjects from the study will not be classified in these groupings.

7.2 Safety areas of interest

Two types of AESIs are defined:

- AESI: ECZTEND defined AESI (defined in the CTP Panel 15). These AEs are marked by the investigator in the eCRF, and these AEs require additional details to be recorded in the eCRF. See Panel 6.
- Tralokinumab ADRs: Defined using Adtralza® Company Core Data Sheet version 5.0, dated 14-Nov-2022. See Panel 7.

The searches described in this document are based on MedDRA version 27.0.

Panel 6: AESI: ECZTEND defined AESI

AESI*	Description
Eczema herpeticum	No additional description
Malignancy	Diagnosed after treatment assignment, excluding basal cell carcinoma, localised squamous cell carcinoma of the skin, and carcinoma in situ of the cervix.
Skin infections	Requiring systemic treatment.
Conjunctivitis**	No additional description
Keratoconjunctivitis**	No additional description
Keratitis**	No additional description

*: as defined in the CTP Panel 15; **: grouped in AESI 'Eye disorders'

Panel 7: Tralokinumab's ADRs

ADRs	Description
Upper respiratory tract infection	Preferred terms: Viral upper respiratory tract infection, Upper respiratory tract infection, Pharyngitis, Nasopharyngitis
Injection site reactions	All preferred terms under the high level term (HLT): Injection site reactions
Eosinophilia	Preferred terms: Eosinophilia, Eosinophil count increased
Conjunctivitis/Conjunctivitis allergic	Preferred terms: Conjunctivitis, Conjunctivitis allergic
Keratitis	Preferred terms: Keratitis

8 References

1. Lott A, Reiter JP. Wilson Confidence Intervals for Binomial Proportions With Multiple Imputation for Missing Data. The American Statistician. 2020;74(2)**:**109-115.

2. Beck LA, Thaçi D, Deleuran M, Blauvelt A, Bissonnette R, de Bruin-Weller M, Hide M, Sher L, Hussain I, Chen Z, et al. Dupilumab Provides Favorable Safety and Sustained Efficacy for up to 3 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. Am J Clin Dermatol. 2020;21(4)**:**567-577.

3. Lachin JM. Fallacies of last observation carried forward analyses. Clin Trials. 2016;13(2)**:**161-168.