Dermatology beyond the skin

Cover Page

Official title: Tralokinumab monotherapy for moderate-to-severe atopic dermatitis ECZTRA 1 (ECZema TRAlokinumab trial no. 1)
LEO Pharma number: LP0160-1325
NCT number: NCT03131648
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Statistical Analysis Plan

Tralokinumab monotherapy for moderate-to-severe atopic dermatitis ECZTRA 1 (ECZema TRAlokinumab trial no. 1)

Phase 3 – Efficacy and safety trial

A randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab monotherapy in subjects with moderate-to-severe atopic dermatitis who are candidates for systemic therapy

LEO Pharma A/S	**Trial ID:**	**LP0162-1325**
	Date:	**20-May-2019**
	Version:	**Final**

1 Statistical Analysis Plan Approval

1.1 Approval Statement

On behalf of LEO, the Biostatistics Lead and the Medical Lead, are authorised to approve the Statistical Analysis Plan.

The QC statistician has by approving this document confirmed that the statistical information has been subject to statistical quality control.

The following persons have approved this Statistical Analysis Plan using electronic signatures as presented on the last page of this document.

PPD

Biostatistics Lead, Global Clinical Operations

PPD

Medical Lead, Medical Science and Safety

PPD

QC Statistician, Biostatistics

2 Statistical Analysis Plan Statements

2.1 Compliance with Good Clinical Practice

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, and E9: Statistical Principles for Clinical Trials).

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3 List of Abbreviations

3.1 List of Abbreviations

AD	atopic dermatitis
ADA	anti-drug antibodies
ADaM	Analysis data model
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BMI	body mass index
BSA	body surface area
DK	Denmark
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI50	At least 50% reduction in EASI score
EASI75	At least 75% reduction in EASI score
EASI90	At least 90% reduction in EASI score
ECG	electrocardiogram
EQ-5D-5L	EuroQoL 5-Dimension Health Questionnaire 5 Level
HADS	Hospital Anxiety and Depression Scale
ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
IMP	investigational medicinal product
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
nAB	neutralising antibodies
NRS	numeric rating scale
PGI-B	Patient Global Impression of Bother
PGI-S	Patient Global Impression of Severity
POEM	Patient Oriented Eczema Measure
Q2W	every 2 weeks
Q4W	every 4 weeks

SAE	serious adverse event
SAP	Statistical Analysis Plan
SCORAD	Scoring Atopic Dermatitis
SCORAD50	At least 50% reduction in SCORAD score
SCORAD75	At least 75% reduction in SCORAD score
SF-36	36-Item Short Form Health Survey
SOC	System Organ Class
TCS	topical corticosteroid
TSQM	Treatment Satisfaction Questionnaire for Medication
WPAI-GH	Work Productivity and Activity Impairment – General Health

4 Introduction

The statistical analysis will be performed as outlined in the Clinical Trial Protocol including amendments.

This Statistical Analysis Plan is prepared before the unblinding of the trial and supplements the Clinical Trial Protocol, which otherwise describes the originally planned statistical analyses of all endpoints in an intended exhaustive manner. The Statistical Analysis Plan contains a more technical and detailed elaboration of some points related to the implementation of the statistical analyses already described in the Clinical Trial Protocol.

In addition, the Statistical Analysis Plan includes supplementary statistical analyses and aspects that are introduced after the latest protocol amendment, of which all are initiated as responses to FDA advices.

Supplementary analyses introduced according to LEO response to CCI letter dated CCI; Ref ID: CCI:

1. A tipping point analysis introduced as a sensitivity analysis number 3 for the primary estimand ('composite') for the primary endpoints (IGA 0/1 and EASI75) and the secondary endpoint (reduction of Pruritus NRS weekly average of at least 4 (yes/no)).
2. Analyses of a new tertiary estimand ('composite') for the continuous secondary confirmatory endpoints (change in SCORAD and change in DLQI). Analyses apply non-responder imputation for subjects who received rescue medication. A tipping point sensitivity analysis is included.

Other supplementary analyses introduced for consistency:

3. The same analysis and tipping point sensitivity analysis as above implemented as a new tertiary ('composite') estimand for the two secondary additional endpoints 'Change from baseline to Week 16 in EASI score' and 'Change from baseline to Week 16 in Worst Daily Pruritus NRS (weekly average)'.

Modification of the US testing hierarchy introduced by LEO in Meeting Background Material for CCI meeting dated CCI; Ref ID: CCI to address CCI letter dated CCI; Ref ID: CCI:

4. A dedicated modified confirmatory testing hierarchy applied in the US submission. The originally specified testing hierarchy is kept for non-US submissions (e.g. to EMA and PMDA).

The first aspect is addressed in section 6.6.2, the 2nd and 3rd are addressed in section 6.6.3 while the 4th aspect is presented in section 6.6.1.

5 Trial Analysis Sets

The trial analysis sets are defined in the protocol and the following modifications to the analysis sets for the initial- and maintenance periods are introduced.

All subjects randomised to initial treatment who were exposed to IMP are included in the full analysis set (FAS) and will be analysed for efficacy up to Week 16 (visit 12). For subjects not exposed to IMP, the decision to withdraw can't be biased by knowledge of the assigned treatment due to the blinding. This definition of the FAS implements the consideration mentioned in the protocol regarding special excluded cases with reference to ICH E9, Section 5.2.1.

The safety analysis set comprises all subjects randomised to initial treatment who were exposed to IMP. The protocol further specifies to exclude subjects from the safety analysis set for whom no post-baseline safety data are available. However, since all subjects receive the first dose of IMP in connection with the Week 0 visit and are subsequently monitored for immediate drug reactions, all exposed subjects are considered to have post-baseline safety data available and no such further exclusions will be made.

The maintenance analysis set is defined in the protocol as all subjects who receive tralokinumab in the initial treatment period and who are re-randomised to maintenance treatment. In addition to this, subjects who are not exposed to maintenance treatment will be excluded from the maintenance analysis set. This follows the same principle that leads to exclusion of unexposed subjects from the full analysis set and is in alignment with ICH E9.

The maintenance safety analysis set comprises all subjects who are re-randomised and receive at least one dose of maintenance treatment.

The open-label safety analysis set comprises all subjects who at any point in time enter the open-label treatment arm and receive at least one dose of open-label treatment.

For the follow-up period the safety follow-up analysis set will be used as the basis for evaluation of adverse events during the follow-up period. It comprises all subjects for whom date of last contact is after the date of exposure end, where exposure end is defined as the Week 52 visit (Week 68 visit for subjects enrolled in short-term extension) for subjects

completing the treatment period, and otherwise the date of permanent discontinuation of IMP for subjects not completing the treatment period. See also section 6.8.2 for further details.

For analysis of efficacy subjects will be included ‘as randomised’.

For analysis of safety, if a subject is mistakenly given an experimental therapy other than that to which they were randomized, they should be analyzed ‘as-treated’, thus included in the group according to the therapy actually received by the subject. The below rules will be applied.

Subjects who received at least one dose of tralokinumab during the initial treatment period will be analysed in the tralokinumab treatment group. Although this may dilute the AE rate in the tralokinumab treatment group slightly by including in the denominator subjects who only received one dose of active treatment, it will ensure that no significant drug reactions to tralokinumab will erroneously be assigned to placebo.

Subjects in the maintenance safety analysis set will be analysed as follows:
Week 16 Tralokinumab responders will be displayed in tables for the maintenance period according to actual treatment defined as:

- Tralokinumab Q2W if
    - subject was randomised to Tralokinumab Q2W and at least one dose of active treatment was administered, or
    - subject was randomised to placebo, but more than half of the administered doses contained active treatment.
- Tralokinumab Q4W if
    - subject was randomised to Tralokinumab Q4W and at least one dose of active treatment was administered, or
    - subject was randomised to placebo but at least one and at most half of the administered doses contained active treatment.
- Placebo if only placebo doses were administered

By assigning subjects randomised to placebo who got at least one active treatment to the Q4W arm a potential safety signal in the Q2W group is not deflated.

Week 16 placebo responders will be displayed in the “Week 16 placebo responders / Placebo” column in summary tables, regardless of actual treatment received. Any deviations from the

planned treatment regimen (i.e. if any active doses are given) will be described as protocol deviations.

6 Statistical Analysis

6.1 Baseline Characteristics

Baseline characteristics will be summarised and listed.

Baseline characteristics for subjects transferred to open-label treatment at Week 16 will be presented by previous treatment and overall.

Duration of AD in years will be calculated as (age at Week 0) minus (age at onset of AD).

The table of concomitant medication at baseline will include medication starting before the first dose of IMP which does not end before the first dose of IMP. For further details, see Section 6.8.3 and Section 6.8.4.

6.2 Disposition

Subject disposition will be summarised and listed.

6.3 Rescue medication

Rescue medication is defined by the following algorithm: Concomitant medications with Dermatitis atopic or Dermatitis infected as the preferred term for the indication and either ATC2 code H02 or D07, or ATC4 code D11AH or Preferred name Methotrexate, Ciclosporin, Azathioprine, Mycophenolate-mofetil, Mycophenolate-sodium, Mycophenolate-acid or Dupilumab.

According to the protocol investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment. Therefore, if rescue medication has start date the same day as an efficacy assessment, then the assumption will be that the assessment is not influenced by the rescue medication, see also Section 6.8.4.

Rescue medication will be summarised separately for the initial and maintenance period. In addition, a summary table of rescue medication by type (topical and systemic) and by overall group (corticosteroids, immunosuppressants and other) will be made.

For subjects continuing with maintenance or open-label treatment at Week 16, the table of rescue medication during initial treatment period will include rescue medication taken (but not necessarily initiated) between the first dose of initial treatment and the first dose of either maintenance or open-label treatment. For subjects who do not continue with maintenance or open-label treatment, the table of rescue medication during initial treatment period will include medications taken after the first dose and before the (nominal) Week 16 visit (or before day 7*16=112 after first dose, in case the (nominal) Week 16 visit did not take place).

The table of rescue medication during the maintenance treatment period will include rescue medication taken (but not necessarily initiated) after the first maintenance dose and exclude rescue medication initiated during the follow-up period.

6.4 Compliance

Compliance will be summarised and listed.

6.5 Exposure

The exposure time during the initial, maintenance and open-label periods, respectively, will be defined as detailed in Section 6.8.2. Exposure time will be summarised and listed.

Patient years of exposure (PYE) for a period will be calculated as the difference between the start date and time and the end date and time for the period divided by 60x60x24x365.25.

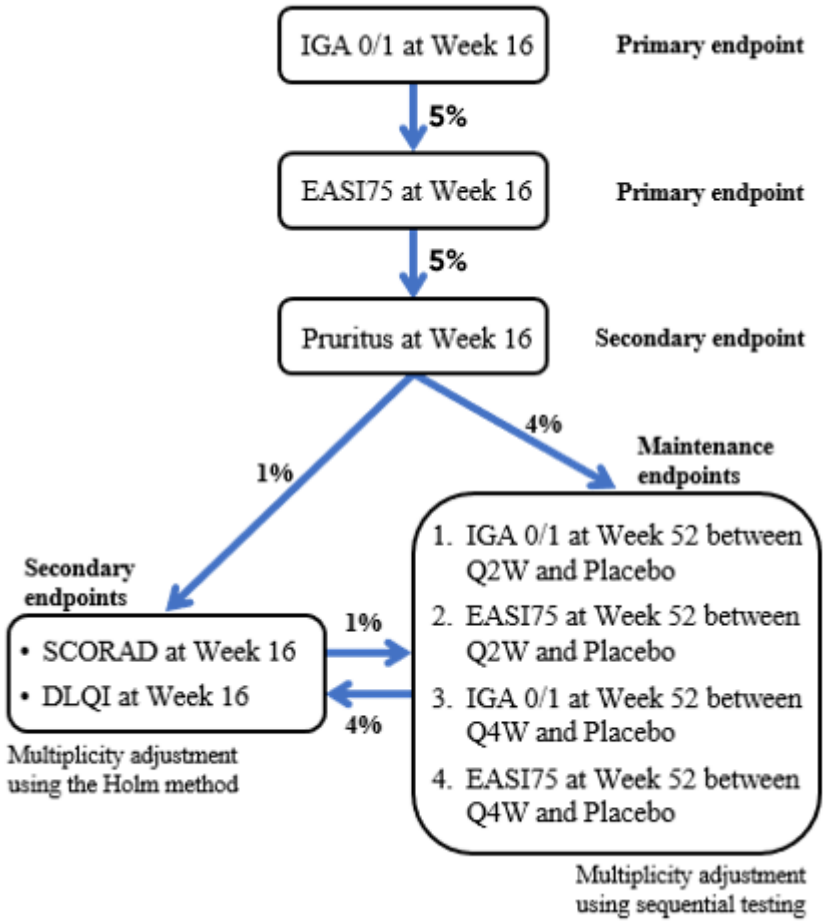
6.6 Analysis of Efficacy

Efficacy will be analysed as described in the Clinical Trial Protocol.

6.6.1 Multiple testing procedure

To control the overall type 1 error rate, the primary analyses of the primary estimands for the primary and secondary endpoints for the initial and maintenance treatment will for the US submission follow a dedicated modified confirmatory testing hierarchy as outlined in Panel 1 below.

Panel 1 Testing procedure for US submission



Arrows indicate order of testing when superiority is shown for all endpoints within a box.
DLQI, Dermatology Life Quality Index; EASI75, at least 75% reduction in Eczema Area and Severity Index score; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks.

IGA 0/1 at Week 16 between tralokinumab and placebo is evaluated at a 5% significance level. If the test is significant, EASI75 at Week 16 between tralokinumab and placebo is evaluated at a 5% significance level. If the second test is also significant, Pruritus at Week 16 between tralokinumab and placebo is evaluated at a 5% significance level.

If all three tests are significant, the significance level (alpha) will be split between the analyses of the 2 secondary endpoints at Week 16 and the analyses of the 2 maintenance endpoints at Week 52. These groups of tests are tested in parallel with alpha=1% for the endpoints at Week 16 and with alpha=4% for the maintenance endpoints at Week 52.

The evaluations of the 2 secondary endpoints at Week 16 between tralokinumab and placebo will use the Holm method (3) for 2 ordered p-values at a 1% significance level to adjust for multiplicity.

The hypotheses for the maintenance treatment endpoints will be tested sequentially in the specified order at the 4% significance level. The next hypothesis will only be tested if the former was significant.

If all p-values for the 2 secondary endpoints at Week 16 are significant, then the hypotheses for the maintenance treatment endpoints can be evaluated at a 5% significance level. Conversely, if all p-values for the maintenance endpoints are significant, then the hypotheses for the 2 secondary endpoints at Week 16 can be evaluated at a 5% significance level.

For non-US submissions, the testing hierarchy defined in the protocol will be applied.

6.6.2 Primary and secondary binary endpoints

Sensitivity analysis 2 for the primary estimand (binary endpoints)

In the sensitivity Analysis 2 for the primary estimand, the protocol specifies that "If subjects have withdrawn due to an AE or due to lack of efficacy, they are still considered non-responders". Such subjects will be identified based on their reason for permanent discontinuation of IMP.

Sensitivity analysis 3 for the primary estimand (binary endpoints)

A tipping point analysis using multiple imputation (MI) as an additional sensitivity analysis (not described in the protocol) for the primary estimand for the primary endpoints (IGA 0/1 and EASI75) and the secondary binary endpoint (reduction of Pruritus NRS weekly average of at least 4 (yes/no); Pruritus NRS ≥ 4) will be done.

The purpose of the sensitivity analysis is to assess the robustness of results of the primary analysis for the primary estimand with respect to the assumption regarding missing Week 16 data among subjects who did not use any rescue medication. The procedure will be as follows: subjects in the tralokinumab arm with missing Week 16 data will per default be considered non-responders while missing Week 16 data (i.e. response yes (=1)/ no (=0)) for subjects in the placebo arm who did not use rescue medication will be imputed from a Bernoulli distribution with parameter p (ranging from 0 to 1). By varying the parameter p, different percentages of placebo subjects will be assumed to be responders (deviating from the

default zero (0) percent of the primary estimand). The tipping-point is then found as the value of p (in the range from 0 to 1) which changes the conclusion (of the primary analysis) from significant to non-significant.

Based on published data from other placebo-controlled clinical trials conducted in subjects with moderate-severe atopic dermatitis[2], the response rate for IGA 0/1, EASI75 and Pruritus NRS ≥ 4 at Week 16 among all placebo subjects is low (in the order of 10% for IGA 0/1 and Pruritus NRS ≥ 4, and 15% for EASI75, respectively). Thus, a tipping-point value (p) above 0.1 for IGA 0/1 and Pruritus NRS ≥ 4 and above 0.15 for EASI75, respectively, is not considered to be clinically plausible. As indicated above, p=0 corresponds to the primary analysis for the primary estimand. The MI procedure will include the following steps for each value of p:

- 100 copies of the dataset will be generated (seed=11109925) and missing Week 16 data will be imputed for subjects in the placebo arm from a Bernoulli distribution with parameter p.

For each of the 100 complete data sets, the difference in response rates will be analysed as specified for the primary analysis for the primary estimand and the estimates and standard errors from the 100 analyses will be combined using Rubin's rule to form a unique point estimate and standard error.

6.6.3 Continuous secondary endpoints

Primary analysis of primary estimand (continuous secondary endpoints)

It is specified in the protocol that the continuous secondary endpoints will be analysed using a repeated measurements model on the post baseline responses up to Week 16. Data collected after permanent discontinuation of IMP or after initiation of rescue medication will not be included in the analysis.

However, some subjects may not have any post-baseline data collected before initiation of rescue medication. To ensure that all subjects are included in the analysis, the baseline value will for these subjects be carried forward as the first post-baseline assessment, corresponding to imputing a change of 0 at the first post-baseline assessment.

Tetriary (composite) estimand (continuous secondary endpoints)

For the continuous secondary endpoints (i.e. change in SCORAD and DLQI), an analysis is introduced where subjects who received rescue medication are considered non-responders. This new analysis aim to estimate the treatment effect for a 'Composite' estimand which is currently not pre-specified in the protocol for the continuous secondary endpoints. Thus, a new tertiary 'Composite' estimand for the continuous secondary endpoints is introduced.

Primary analysis for the tertiary (composite) estimand (continuous secondary endpoints): Data retrieved at Week 16 for subjects who have permanently discontinued IMP prior to Week 16 will be included in the analysis. Subjects who prior to the Week 16 visit have received rescue medication will be considered non-responders by using worst observation carried forward (including the baseline value).

Missing Week 16 data among subjects who did not use rescue medication will be imputed using MI (100 copies of the dataset, seed=11109925) assuming missing at random (MAR) within arms (based on sequential use of an ANCOVA model for Week 2, 4, 6, .. and 16). For subjects who dropout without any use of rescue medication, missing data at subsequent visits will be imputed under the assumption that the subject adheres to the randomised treatment regimen, i.e. the stepwise imputation model will be estimated based on available data from all subjects but excluding individual subject data captured after initiation of rescue medication or permanent discontinuation of IMP. For each of the 100 imputed datasets, the continuous secondary endpoint will be analysed using an ANCOVA model with effects of treatment, region, baseline disease severity (IGA 3 or 4), and baseline value. The estimates and standard errors from the 100 analyses will be combined using Rubin's rule to form a unique point estimate and standard error.

As a sensitivity analysis for the tertiary estimand, a tipping point analysis using MI will be performed with the purpose to assess the robustness of results of the primary analysis for the tertiary estimand with respect to the MAR assumption regarding missing Week 16 data among subjects who did not use any rescue medication. The tipping analysis will assess how severe the departure from the MAR assumption in the tralokinumab arm has to be in order to impact the results (i.e. changes the conclusion of primary analysis of the tertiary estimand) from significant to non-significant).

The tipping point analysis will be performed using the MAR imputed Week 16 data from primary analysis of the tertiary estimand. For each of the 100 imputed datasets, Δ will be added to the imputed values for subjects in the tralokinumab arm ($\Delta = 0$ implies MAR) and thereby the imputed values will be 'shifted' by Δ. Each of the 100 modified imputed datasets

will then be analysed in the same way as for the primary analysis for the tertiary estimand. The tipping-point is then found as the value of Δ which changes the conclusion (of the primary analysis) from significant to non-significant and will be judged from a clinical point of view.

The implications of the missing not at random assumptions will be compared to the implication of the missing at random assumptions by visual inspection.

Tetriary (composite) estimand (continuous additional secondary endpoints)

The two continuous secondary additional endpoints 'Change from baseline to Week 16 in EASI score' and 'Change from baseline to Week 16 in Worst Daily Pruritus NRS (weekly average)' will be analysed as described for the two continuous secondary endpoints above, including the tipping point sensitivity analysis.

6.6.4 Multiple imputation

For the analysis of the primary and secondary endpoints, multiple imputation will be carried out as specified in the protocol, using SAS PROC MI. For multiple imputations related to the treatment policy estimand and the hypothetical estimand sensitivity analyses, the seed 11109925 will be used. The remaining seeds are specified in the protocol.

When performing mulitiple imputation of continuous parameter values, imputed values at visits prior to Week 16 outside the relevant parameter scale shall be used as is. Values imputed at Week 16 shall be truncated to the nearest upper or lower bound on the given scale. For example, negative imputed EASI values at Week 16 will be set to 0.

For imputation of IGA values, the LIKELIHOOD=AUGMENT option will be used (1).

For imputation of IGA values, it may occur that the observed data from which the imputation model is fitted does not contain all levels of the IGA predictors necessary for the imputation. For example, the imputation model for IGA values at Week 8 will be based on observed data from the subset of subjects with observed IGA values at both Week 6 and Week 8. If only the IGA values (0,1,2,3) are observed at Week 6 in this subset of subjects, the imputation model will not be able to predict IGA values at Week 8 for a subject with an IGA value of 4 at Week 6. To avoid this situation, in this specific example IGA values of 3 and 4 at Week 6 will be combined into a single category for the purpose of the imputation. In general, if this situation

arises, IGA categories will be combined into a single category at the specific visit for the purpose of the specific imputation, according to the rules in Table 1.

Table 1: Adjacent IGA categories combined in case of missing predictors in observed data

IGA value(s) missing in imputation model	**IGA categories combined**
0	(0,1)
1	(0,1)
2	(2,3)
3	(2,3)
4	(3,4)

6.6.5 Secondary and other efficacy analysis

Reduction of Worst Daily Pruritus NRS weekly average of at least 4

The analyses will be based on subjects in the FAS with a baseline Pruritus NRS weekly average of at least 4.

The binary endpoint was to be analysed as described for the primary endpoint EASI75 using all three estimands. It is however expected that subjects will not fill in the eDiary when they have discontinued treatment, and it is considered likely, there will be no nominal Week 16 data available for discontinued subjects. If this is the case, the primary analysis of the tertiary estimand will not be estimated for this endpoint. The corresponding sensitivity analysis for the tertiary estimand, analysing subjects with missing Week 16 data as non-responders, while otherwise using observed data for the remaining subjects, will still be conducted.

Calculation of Weekly average of pruritus NRS

The weekly average will only be calculated if at least 4 assessment are available. When calculating the baseline value for the weekly average of Worst Daily Pruritus, the daily assessments in the 7 days preceding the randomisation will be used, including the day of randomisation.

For the initial treatment period, the NRS weekly average for Week 1 will be calculated based on scores recorded on day 1 to day 7 (where day 0 is the day of the first dose). Similarly, for Weeks 2 to Week 15, the weekly average for Week x will be calculated based on scores recorded on day 7*x-6 to day 7*x (where day 0 is the day of first dose). To account for the actual day maintenance or open-label treatment is initiated, the Week 16 weekly average will instead be based on the last 7 days before (and including) the day of the Week 16 visit, thus

ensuring that the Week 16 weekly average is based on data from the initial treatment phase only, and also ensuring alignment in timing with other Week 16 efficacy endpoints. Also, for the calculation of Week 1 to Week 15 weekly averages, any scores recorded after the Week 16 visit date will be disregarded (only relevant if Week 16 visit is out of window).

For Week 17 of the maintenance treatment period, the weekly average will be based on the first 7 days after (not including) the Week 16 visit. For Week 18 to Week 52 of the maintenance treatment period, the weekly average for Week x will be calculated based on scores recorded on day 7*x-6 to day 7*x (where day 0 is the day of the first dose). Any scores recorded after initiation of open-label treatment will be disregarded.

PGI-B and PGI-S

For the PGI-B and PGI-S, which are not numerical, the worst score recorded during the week will be presented instead of weekly averages. The worst score will be derived if at least one measurement is available for the week in question. The same rules regarding visit windowing apply as for weekly average pruritus NRS described above. The daily scores will be presented graphically.

Percentage change in EASI score, initial treatment period

In addition to the repeated measurements analysis of absolute reduction in EASI score during the initial treatment period which was planned in the protocol, the same analysis will be conducted for the percentage change from baseline in EASI scores during the initial treatment period.

Subgroup analyses

To access the consistency in response rate across subgroup the following subgroup analyses will be performed for the primary estimand:

- IGA 0/1 by baseline IGA
- IGA 0/1 by region
- EASI75 by baseline IGA
- EASI75 by region

Efficacy analyses open-label period

For the open-label treatment period IGA, EASI75, EASI and SCORAD will be summarised by visit and initial treatment for subjects who transferred to open-label treatment at Week 16,

and by week since transfer to open-label and at Week 52, by previous maintenance treatment for subjects who transferred to open-label treatment after Week 16. IGA, EASI and SCORAD for subject who transferred to open-label treatment at Week 16 and IGA for subject who transferred to open-label treatment after Week 16 will be presented in figures.

Scoring of PROs

POEM	Scored according to: https://www.nottingham.ac.uk/research/groups/cebd/documents/methodological-resources/poem-for-self-completion.pdf
DLQI	Scored according to: http://sites.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi/dlqi-instructions-for-use-and-scoring/
EQ-5D-5L	Index values calculated according to: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/ The UK value sets will be used.
HADS	The HADS consists of 14 items, 7 of which are related to anxiety and 7 related to depression. The maximum score is 21 for each subscale (anxiety and depression). If one question is missing within a subscale, the response to that question will be imputed as the mean of the remaining questions in that subscale. If more than one question is missing within a subscale, the subscale is considered missing.
SF-36	Scored by QualityMetric Health Outcomes(tm) Scoring Software 5.0 Q provided with license.
WPAI-GH	Scored according to: http://www.reillyassociates.net/WPAI_Scoring.html
TSQM v.II	Scored according to User Manual for the Treatment Satisfaction Questionnaire for Medication (TSQM) 1.0 provided with license.

PROs in the open-label period

By mistake PROs are reported in some instances for subjects in the open-label period. These data will be presented in listings only.

Missing baseline assessments

When the baseline value is missing, endpoints concerning a change from baseline will not be derived, and such subjects will be excluded from the analysis. Since the missingness of baseline values are unrelated to the assigned treatment, bias should not be a concern with this approach.

6.7 Analysis of Safety

6.7.1 Adverse Events

Adverse events will be summarised and listed.

Assignment of AEs to periods

An adverse event will be assigned to a given period (initial, maintenance, open-label or follow-up) if the start date is after the start date and before the end date of that period (see Section 6.8.2, Table 4).

For AEs with start day on the same day as the first dose was given, only AEs starting after the first dose was given will be considered treatment emergent and assigned to the initial treatment period.

AEs with start date on the same day as the first dose of maintenance treatment will be assigned to the initial or maintenance period depending on whether the AE started before or after the dose was given.

AEs with start date on the same day as the first dose of open-label treatment will be assigned to the previous treatment period (can be initial or maintenance) or assigned to the open-label period depending on whether the AE started before or after the dose was given.

AEs starting on the day of exposure end (as defined in Section 6.8.2) will be assigned to the last treatment period.

For handling of incomplete start dates of adverse events, see Section 6.8.3.

Sort order of AE tables

Generally, AE tables by system organ class and/or preferred term will be sorted by decreasing number of affected subjects:

- For the initial treatment period, AE tables will be sorted by decreasing number of affected subjects in the Tralokinumab Q2W group.
- For the maintenance treatment period, AE tables will be sorted by decreasing total number of affected subjects in the Tralokinumab treatment groups (sum of Q2W and Q4W).
- For the entire treatment period, AE tables will be sorted by decreasing number of affected subjects in the “Tralokinumab total” group.

- For the follow-up period, AE tables will be sorted by decreasing total number of affected subjects in the Tralokinumab treatment groups (sum of Q2W, Q4W and Q2W+optional TCS).

6.7.2 Vital signs

Vital signs will be summarised and listed.

For the summary tables of vital signs by visit, the last pre-dose vital sign assessment will be presented. If no dosing occurs at a visit, the last assessment recorded at the visit will be presented. For the first 3 IMP dosing visits in both the initial and open-label treatment period, subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, these measurements will only be listed.

6.7.3 ECG

ECG data will be summarised and listed. The overall central evaluation of ECG will be presented using shift tables.

6.7.4 Laboratory Data

Laboratory data will be summarised and listed.

For the laboratory values, if the value is below the lower limit of quantification, half of the lower limit will be used for quantitative summaries. If the value if above the upper limit of quantification, the upper limit value will be used.

If more than one laboratory value is reported for the same visit, the latest value will be used in summary statistics and analyses.

Potentially clinically significant values will be defined as displayed in Table 2.

Table 2: Potentially clinically significant biochemistry and haematology values

Protocol Lab parameter	**SI Unit**	**PCS low**	**PCS High**
Biochemistry			
Sodium	mmol/L	< 129 mmol/L, < 125 mmol/L	> 160 mmol/L
Potassium	mmol/L	< 3 mmol/L, < 2.5 mmol/L	> 6.5 mmol/L, > 7.5 mmol/L

Creatinine	umol/L	N/A	> 1.5xULN, > 3xULN
Calcium	mmol/L	< 1.9 mmol/L	> 3.0 mmol/L, > 3.5 mmol/L
Alkaline phosphatase	U/L	N/A	> 3xULN
Aspartate aminotransferase	U/L	N/A	> 3xULN, > 5xULN, > 10xULN, > 20xULN
Alanine aminotransferase	U/L	N/A	> 3xULN, > 5xULN, > 10xULN, > 20xULN
Bilirubin	umol/L	N/A	> 2xULN
Cholesterol	mmol/L	N/A	> 6.2 mmol/L
LDL cholesterol	mmol/L	N/A	> 4.1 mmol/L, > 4.9 mmol/L
HDL cholesterol	mmol/L	N/A	> 1.6 mmol/L
Triglycerides	mmol/L	N/A	> 2.3 mmol/L, > 5.6 mmol/L
Glucose (non-fasting)	mmol/L	< 3.9 mmol/L	>11.1 mmol/L
Haematology			
Haemoglobin	g/L	<110 g/L, < 80 g/L	> 185 g/L for male, > 165 g/L for female
Neutrophils, absolute count	10^9/L	< 1.5 10^9/L, < 1.0 10^9/L, < 0.5 10^9/L	N/A
Lymphocytes, absolute count	10^9/L	< 1.0 x 10^9/L, < 0.5 x 10^9/L	> 5.0 x 10^9/L
Monocytes, absolute count	10^9/L	< 0.1 x 10^9/L	> 0.8 x 10^9/L
Eosinophils, absolute count	10^9/L	N/A	> 1.5, > 5.0
Basophils, absolute count	10^9/L	N/A	> 0.2
Thrombocytes	10^9/L	< 100 x 10^9/L, < 30 x 10^9/L, < 10 x 10^9/L	> 450 x 10^9/L

PCS: potentially clinically significant; ULN: Upper limit of normal, i.e. upper limit of normal reference range.

6.7.5 Urinalysis

Urinalysis data will be summarised and listed.

Potentially clinically significant values will be defined as displayed in Table 3.

Table 3 Potentially clinically significant urinalysis values

Protocol lab parameter (ACM lab parameter)	**SI Unit**	**PCS low**	**PCS High**

Erythrocytes	/HPF	N/A	> 3, >10, >25, >30
Leucocytes	/HPF	N/A	> 10
Casts (Hyaline casts)	/LPF	N/A	> 2
Casts (WBC casts)	/LPF	N/A	Few, Moderate, Many
Casts (RBC casts)	/LPF	N/A	Few, Moderate, Many
Casts (Waxy casts)	/LPF	N/A	Few, Moderate, Many
Casts (Granular casts)	/LPF	N/A	Few, Moderate, Many

PCS: potentially clinically significant; HPF: high power field; LPF: low power field; ULN: Upper limit of normal, i.e. upper limit of normal reference range.

6.7.6 Staphylococcus aureus

Staphylococcus aureus colonization based on skin swab samples will be summarised and listed.

6.7.7 Pharmacokinetics and anti-drug antibodies

Pharmacokinetics and anti-drug antibodies data will be summarised and listed.

6.7.8 Biomarkers

The small panel biomarkers; periostin, DPP4, hBD2, TARC, IL-13, IL-17, IL-22, and IgE will be summarized and listed. Other potential biomarkers from the small panel will be presented in a separate report.

As described in the protocol the large panel biomarkers will be presented in a separate report.

6.7.9 Biopsy biomarkers

Skin biopsies will be taken at selected trial sites.

The Histology/immunohistochemistry markers; epidermal thickness, FLG, CD3, CD1a, and CD11c and gene expression analysis; IFN, IL-13, CCL17, CCL22, IL-17A, IL-22, S100A12, and LOR will be summarised and listed. All other skin biopsy markers will be presented in a separate report.

6.8 General Principles

6.8.1 Baseline value

Unless otherwise specified, the baseline value is defined as the latest pre-dose assessment.

6.8.2 Definition of trial periods and date of permanent discontinuation of IMP

Date of permanent discontination of IMP
Defined for subjects who have a reason for permanent discontinuation of IMP recorded. Defined as date of early termination visit (if existing), otherwise date of the last visit, excluding safety follow-up and nominal Week 16 visit.

Exposure start
Date and time of first dose.

Exposure end (subjects not enrolled in short term extension)
Date of Week 52 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.

Exposure end (subjects enrolled in short term extension)
Date of Week 68 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.

At DBL 1 all data up to and including LSLV, April 11, 2019 is included. For subjects ongoing at DBL 1 (i.e. subjects ongoing in short term extension), exposure end will be set to date of data cut-off April 11, 2019.

Trial periods
The time from exposure start to exposure end will be divided into initial period, maintenance period and open-label period, and remaining time after exposure end will be assigned to the follow-up period as shown in Table 4 (ADaM variable APHASE). The ADaM variable APERIODC will indicate the latest treatment (initial, maintenance or open-label) at any given time point, thus not including a follow-up period (Table 5).

Table 4: Start and end time of trial periods (ADaM variable APHASE).

APHASE	**Start of period**	**End of period (only if start date exists)**
Initial period	Exposure start	Date and time (minus 1 second) of first maintenance dose (if existing) else Date and time (minus 1 second) of first open-label dose (if existing) else Exposure end
Maintenance period	Date and time of first maintenance dose (if existing)	Date and time (minus 1 second) of first open-label dose (if existing) else Exposure end
Open-label period	Date and time of first open-label dose (if existing)	Exposure end
Follow-up period[1]	Exposure end (plus 1 second)	Date of safety follow-up visit (if existing) at time 23:59:00 else Date of last contact at time 23:59:00

1) Only applicable if date of last contact is not equal to date of exposure end.

Table 5: Start and end time of trial periods (ADaM variable APERIODC).

APERIODC	**Start of period**	**End of period (only if start date exists)**
Initial period	Exposure start	Date and time (minus 1 second) of first maintenance dose (if existing) else Date and time (minus 1 second) of first open-label dose (if existing) else Date of last contact at time 23:59:00
Maintenance period	Date and time of first maintenance dose (if existing)	Date and time (minus 1 second) of first open-label dose (if existing) else Date of last contact at time 23:59:00
Open-label period	Date and time of first open-label dose (if existing)	Date of last contact at time 23:59:00

6.8.3 Incomplete recordings

Adverse events

If the AE start day is missing, but AE start month and year are not missing, the following rules apply:

- If the year and month of the AE start is before the year and month of the exposure start, or if the AE end date is complete and before the exposure start, the AE will not be considered treatment emergent.
- If the year and month of the AE start is the same as the year and month of the exposure start, the AE will be considered treatment emergent and assigned to the initial treatment period, unless the AE has a complete end date which is before exposure start.
- If the year and month of the AE start is after the year and month of exposure start, it will be assumed that the AE started on the first day of the month and the AE will be assigned to the initial, maintenance, open-label or follow-up period accordingly.

If the AE start month is missing, but AE start year is not missing, the following rules apply:

- If the year of the AE start is before the year of the exposure start, or if the AE end month is not missing and before the month of the exposure start, or if the AE has a complete end date which is before the exposure start date, the AE will not be considered treatment emergent.
- If the year of the AE start is the same as the year of the exposure start, the AE will be considered treatment emergent and assigned to the initial treatment period, unless the AE end month is not missing and before the month of the exposure start or the AE has a complete end date which is before the exposure start date.
- If the year of the AE start is after the year of exposure start, it will be assumed that the AE started on the 01 January and the AE will be assigned to the initial, maintenance, open-label or follow-up period accordingly.

Concomitant medication

For incomplete start dates of concomitant medication, the following rules apply:

- If a medication start day is missing, but start month and year is not missing, it will be assumed that the start day is the first day of the month. If the medication start day and month is missing, but start year is not missing, it will be assumed that the start day is

01 January. If the medication start day, month and year is missing, it will be assumed that the medication was started before study start, and the date will appear as missing in the data.

For incomplete end dates of concomitant medication, the following rules apply:

- If a medication end day is missing, but end month and year is not missing, it will be assumed that the end day is the last day of the month. If the medication end day and month is missing, but end year is not missing, it will be assumed that the end day was 31 December. If the medication end day, month and year is missing, it will be assumed that the medication was ongoing at the end of the study, and the date will appear as missing in the data.

6.8.4 Conventions regarding time of day for efficacy assessments and concomitant medication

Efficacy assessments

For the purpose of assigning trial periods to efficacy assessments, the convention will be that efficacy assessments are performed at time 00:00:00 in the morning. As a consequence, efficacy assessments performed on the day of transfer between two periods will be assigned to the first of the two periods.

Concomitant medication

For the purpose of associating concomitant medication with trial periods, the convention will be that the start time of day of concomitant medications is 23:59:59, and end time is 00:00:00, unless the start day is equal to the end day in which case both start and end time will be assumed to be 23:59:59. As a consequence, rescue medication starting on the day of transfer between two periods will be associated with the latter period only, and rescue medication ending on the day of transfer between two periods will be associated with the first period only (unless the start day is equal to the end day).

Unlike adverse events which are assigned to a single period based on their start date only, a concomitant medication can be associated with more than one period.

6.8.5 Treatment Completers

A subject who has not permanently discontinued IMP before Week 52 will be defined as a treatment completer.

6.8.6 Early termination and unscheduled visits

When no data is available from a certain scheduled post-baseline visit for a particular subject, data from early termination visits and unscheduled visits have the potential to replace data from that particular scheduled visit in data summaries, provided the data is collected between 6 days before and 7 days after the planned time point for the scheduled visit, as displayed below.

Visit (Target day)	**Visit window (Day is date of assessment minus date of first dose)**
Week 2 (Day 14)	Day 8 to 21
Week x (Day 7*x) (where x= 4, 6, ..., 52)	Day 7*x-6 to 7*x+7
Week x (Day 7*x) (where x=54, 56, ..., 68) (only applicable for subjects enrolled in short-term extension)	Day 7*x-6 to 7*x+7
Safety follow-up	106-119 days after last dose

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.

6.8.7 Handling of Drop-outs and Missing Values

Missing values will be handled as described in the Clinical Trial Protocol.

Week 16 LOCF

As specified in the protocol, a sensitivity analysis of the primary endpoint will impute Week 16 missing values using LOCF. The LOCF value will be defined as the last assessment obtained up to and including day 7*16+7=119 after the first dose, i.e. the last assessment before or within the window for mapping an early termination visit to Week 16.

6.8.8 Treatment Labels

Table 6: Treatment labels for the clinical trial report text and tables

Period	Label Used in Text	Label Used in Tables	Order in Table
Initial period	Tralokinumab Q2W	Tralokinumab Q2W	1
Initial period	Placebo	Placebo	2
Maintenance period	Week 16 Tralokinumab responders: Tralokinumab Q2W	Week 16 Tralokinumab responders: Tralokinumab Q2W	1
Maintenance period	Week 16 Tralokinumab responders: Tralokinumab Q4W	Week 16 Tralokinumab responders: Tralokinumab Q4W	2
Maintenance period	Week 16 Tralokinumab responders: Placebo	Week 16 Tralokinumab responders: Placebo	3
Maintenance period	Week 16 Placebo responders: Placebo	Week 16 Placebo responders: Placebo	4
Open-label period	Tralokinumab Q2W + optional TCS	Tralokinumab Q2W + optional TCS	1

7 References

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3. Holm S. A simple sequentially rejective multiple test procedure. Scan J Stat. 1979;6(2):65-70.

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