Cover Page

Study title: Tralokinumab in combination with topical corticosteroids in Japanese subjects with moderate-to-severe atopic dermatitis ECZTRA 8 (ECZema TRAlokinumab trial no. 8)
LEO Pharma number: LP0162-1343
NCT number: NCT04587453
Date: 15-Jun-2021

Statistical Analysis Plan

LP0162-1343

Tralokinumab in combination with topical corticosteroids in Japanese subjects with moderate-to-severe atopic dermatitis
ECZTRA 8 (ECZema TRAlokinumab trial no. 8)

Phase 3 – efficacy and safety trial

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

LEO Pharma A/S	**Trial ID:**	**LP0162-1343**
	Date:	**15-Jun-2021**
	Version:	**1.0**

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 , MSc

Biostatistics Lead, Medical Science

PPD , MD

Medical Lead, Medical Science

PPD MSc

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

AD	atopic dermatitis
ADA	anti-drug antibodies
ADaM	analysis data model
AE	adverse event
AxMP	auxiliary medicinal product
BSA	body surface area
CRF	case report form
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI75	at least 75% reduction in EASI score
ECG	electrocardiogram
FAS	full analysis set
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator's Global Assessment
IGA 0/1	IGA response of 0 (clear) or 1 (almost clear)
IMP	investigational medicinal product
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
NRS	numeric rating scale
POEM	Patient Oriented Eczema Measure
PYE	patient years of exposure
Q2W	every 2 weeks
QC	quality control
SAP	statistical analysis plan
SCORAD	Scoring Atopic Dermatitis
SOC	(MedDRA) system organ class
SOP	standard operating procedure
TCS	topical corticosteroid(s)

4 Introduction

The statistical analysis will be performed as outlined in the clinical trial protocol.

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 analysis already described in the clinical trial protocol.

In addition, the statistical analysis plan includes supplementary statistical analyses and aspects that are introduced after the protocol.

New analyses:

The analyses of the other endpoints, reduction from baseline to Week 16 of DLQI≥4 among subjects with baseline DLQI≥4 and reduction from baseline to Week 16 of POEM score ≥4 points in subjects with baseline POEM score ≥4, will be analysed by applying the composite estimand. In addition, the same endpoints will be evaluated at each scheduled visit/assessment up to Week 12.

A repeated measurements analysis of the change from baseline in EASI score from baseline to Week 16 has been added.

Trial completers will be defined as stated in the protocol. Reason for not completing the trial will be assessed using the alternatives listed for not attending the safety follow-up visit except for the alternatives ‘transferred to 1337’ and ‘safety follow-up information collected at nominal Week 16 visit’.

A descriptive presentation of IGA 0/1 and EASI75 at week 16 by baseline IGA have been added.

5 Trial analysis sets

The trial analysis sets are defined in the protocol and the following modifications to the analysis sets are introduced.

All subjects who are randomised to treatment and exposed to IMP will be included in the full analysis set (FAS) and will be analysed for efficacy up to Week 16. Exclusions from the FAS can be considered in special cases as described in the ICH E9 guideline, Section 5.2.1. If it is

decided to exclude a randomised and exposed subject from the FAS, a justification addressing ICH E9 will be given.

As stated in the protocol, a safety analysis set will be defined as all randomised subjects who receive IMP.

In addition to the analysis sets defined in the protocol, a safety follow-up analysis set will be used as the basis for evaluation of adverse events during the safety 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 16 visit for subjects completing the treatment period, and otherwise the date of permanent discontinuation of IMP (tralokinumab/placebo) for subjects not completing the treatment period. See also Section 6.8.2 for further details.

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

For analysis of safety, subjects will be analysed ‘as treated’ according to the following rule: subjects who received at least one dose of tralokinumab 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.

The decisions regarding inclusion/exclusion of subjects from the trial analysis sets will be documented in the analysis set definition document before breaking the randomisation code.

6 Statistical Analysis

6.1 Demographics and baseline characteristics

Demographics and baseline characteristics will be summarised and listed.

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. Also, a table of concomitant medication during the treatment period will be included. Concomitant medication with start date equal to the day of exposure end will be assigned to the safety follow-up period, see Section 6.8.4. For handling of incomplete dates, see Section 6.8.3.

6.2 Disposition

Subject disposition will be summarised and listed.

6.3 Treatment compliance

Compliance will be summarised and listed. If a dose is received partly, e.g. only one injection, then this dose is treated as a compliant (non-missed) dose in the summary tables.

In case of permanent discontinuation of IMP, only doses missed before permanent discontinuation of IMP will be included in the summary tables.

6.4 Exposure

The exposure time will be defined as detailed in Section 6.8.2. Exposure time will be summarised and listed.

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

6.5 Rescue medication

Rescue treatment will be summarised and listed. Initiation of rescue treatment will be presented using a cumulative proportions plot over time instead of the Kaplan-Meier plot described in the protocol.

The table of rescue medication 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).

6.6 Analysis of efficacy

Efficacy will be analysed as described in the clinical trial protocol.

Calculation of Weekly average of pruritus NRS

The weekly average will only be calculated if at least 4 out of the 7 weekly assessment are available and otherwise set to missing. In case of several entries on the same day, the worst observation of that day will be used.

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 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).

For Week 16, the weekly average will be calculated based on the scores recorded on the day of the Week 16 visit and the 6 days prior to that day.

Calculation of Weekly average of Eczema-related Sleep NRS

Weekly averages of Eczema-related Sleep NRS will be calculated using the same rules as for the weekly averages of pruritus NRS. As for the Worst Daily Pruritus NRS, in case there are several Eczema-related Sleep NRS assessments at the same date only the worst will be used.

6.6.1 Primary efficacy endpoints

Primary analysis for the secondary estimand

As described in the protocol, imputation of missing data at Week 16 will be done using multiple imputations within 4 groups defined according to treatment group and whether or not subjects have permanently discontinued IMP prior to Week 16 assuming data is missing at random (MAR). Imputation within one or more groups may not be feasible if too few data is available. If this is the case, the primary analysis will not be conducted and will be replaced by the corresponding sensitivity analysis where subjects with missing data will be imputed as non-responders.

6.6.2 Key secondary efficacy endpoints:

Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to Week 16 will be based on subjects in the FAS with a baseline Pruritus NRS weekly average of at least 4.

The binary endpoint is planned to be analysed as described for the primary endpoint EASI75 using the two 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 secondary estimand ('treatment policy') will not be performed for this endpoint. The corresponding sensitivity analysis for the secondary estimand, analysing subjects with missing Week 16 data as non-responders, while otherwise using observed data for the remaining subjects, will still be conducted.

SCORAD

For the calculation of SCORAD, the protocol states that dryness is evaluated on uninvolved areas. This means that if a subject has an extent, i.e. total body surface area (BSA) affected by AD, of 100% then there is no area to score. In the event that dryness is missing and extent is 100% then a dryness score of 0 (none/absent) will be imputed.

6.6.3 Multiple imputation

For the analysis of the primary and key secondary endpoints, multiple imputation will be carried out, as specified in the protocol, using SAS PROC MI. Unless otherwise specified in the protocol, the seed 11109943 will be used.

When performing multiple 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)

6.6.4 Other endpoints and patient-reported outcomes:

The two binary other endpoints, reduction from baseline to Week 16 of DLQI≥4 among subjects with baseline DLQI≥4 and reduction from baseline to Week 16 of POEM score ≥4 points in subjects with baseline POEM score ≥4, will be analysed as described for the primary analysis of the primary estimand ('composite') for the primary efficacy endpoints. In addition, the same endpoints will be evaluated at each scheduled visit/assessment up to Week 12.

Amount of TCS used

The amount of TCS used will be calculated as specified in section 6.6.6 and analysed in two ways, reflecting the two consumption assumptions. The primary analysis will be using the most conservative assumption that all missing tubes were fully used. The second assumption will be used as a sensitivity analysis, reflecting the primary analysis's extreme opposite, that all non-returned tubes were not used. The method used for analysis will be the one specified in the protocol. Additionally, descriptive histograms of both consumption assumptions will be produced.

Number of days without topical treatment use

The number of days without topical treatment use (collected as Patient Days of Topical Treatment Use in the eDiary) will be determined over 1-week periods from Week 0 until Week 16 and will be summarised over time by treatment group as specified in the protocol. Number of days without topical treatment use will be calculated using the same rules as for the Worst Daily Pruritus NRS (weekly average). In addition, a new binary endpoint '5-7 days without topical treatment use' will be introduced. This new endpoint will be evaluated by week and by treatment group as described for the primary analysis of the primary estimand ('composite') for the primary efficacy endpoints.

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/

6.6.5 Exploratory analyses

Reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 from baseline to each scheduled assessment up to Week 15 will be based on subjects in the FAS with a baseline Pruritus NRS weekly average of at least 4.

Change from baseline in EASI score

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

Subgroup analyses

To assess the consistency of the number of responders for the primary composite estimand across subgroups, IGA 0/1 and EASI75 will be presented descriptively by baseline IGA.

6.6.6 AxMP (TCS) accountability

For each subject, the weight of TCS used for a given visit interval (WGTUSED) will be calculated as the difference between the weight of the tubes dispensed (WGTDISP) and the weight of the returned tubes (WGTRET):

- if WGTRET ≤ WGTDISP then WGTUSED=WGTDISP-WGTRET
- if WGTRET > WGTDISP then WGTUSED = 0.

All tubes dispensed at a visit are assumed to be returned at the subsequent visit where new tubes are dispensed. The amount of TCS used from these tubes will be attributed to the period between these two visits.

When tubes are not returned as specified in the protocol, the following rules will be applied:

- If a dispensed tube is not returned at all and the subject remains in the study, two different approaches will be applied to explore two extreme assumptions:

    1. It will be assumed that the missing tube has been fully used by the subject in the period between the date the tube was dispensed, and the date of the next subsequent visit attended by the subject. Estimated content (100 g) for the kit number will be used as a contribution to the WGTRET.

2. It will be assumed that the missing tube has not been used at all by the subject in the period between the date the tube was dispensed, and the date of the next subsequent visit attended by the subject, i.e. contribution from the tube to the WGTRET is set to 0.

- In the case where tubes from the last dispensing visit are not returned due to the subject being withdrawn from the trial, the amount of TCS used from these tubes will not be calculated (i.e. set to missing).

If a subject does not attend a planned visit, daily usage (DAYUSE) is calculated for the period between the tubes being dispensed and the subsequent dispensing visit, i.e. DAYUSE=WGTUSED/DURATION where DURATION =ENDDATE (date of the subsequent dispensing visit)-STARTDATE (date of the tubes being dispensed). The amount of TCS used for each visit in the period (missing visit(s) and the first visit after the tubes being dispensed) is calculated by multiplying daily usage (DAYUSE) by the number of days between the visit and the previous visit. For missing visits, the planned dates according to the trial schedule will be used.

6.7 Analysis of Safety

As specified in the protocol, the analysis of safety will be based on the safety analysis set and the safety follow-up analysis set.

6.7.1 Adverse events

Adverse Events will be summarised and listed. The summaries will be split into the treatment period and the safety follow-up period. Adverse Events occurring prior to the first dose will only be listed.

Assignment of AEs to periods

An Adverse Event (AE) will be assigned to a given period (treatment period or safety 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 treatment period.

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

For handling of incomplete start dates of AEs, see Section 6.8.3.

Sort order of AE tables

Generally, AE tables by system organ class and/or preferred term will primarily be sorted alphabetically by SOC, and the preferred terms within the SOC will be sorted by decreasing number of events found in any of the treatment groups. The treatment group itself will not be considered in the sorting.

Other adverse events of interest

A MedDRA search on all reported AEs will be made to capture AEs belonging to injection site reactions. The MedDRA search to capture this safety area of interest was performed using the following high-level terms (based on primary and secondary terms): 'administration site reactions NEC', 'application and instillation site reactions', and 'injection site reactions'. As only primary terms are available in SDTM data, a list of preferred terms included within the high-level terms are used to account for secondary terms. The list has been reviewed prior to unblinding of the trial.

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, subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 30 minutes with vital signs taken at every 30 minutes or until stable, whichever is later. These measurements will be listed.

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

Table 2: Potentially clinically significant vital signs values

Protocol parameter	SI unit	PCS low	PCS high
Systolic blood pressure	mmHg	<90 and decrease from baseline ≥20	≥180 and increase from baseline ≥20
Diastolic blood pressure	mmHg	<50 and decrease from baseline ≥15	≥105 and increase from baseline ≥15
Pulse	beats/min	<50 and decrease from baseline ≥15	≥120 and increase from baseline ≥15

Abbreviations: PCS=potentially clinically significant.

6.7.3 Electrocardiogram

Electrocardiogram (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 is 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 and time point, the latest value will be used in summary statistics and analyses.

Shift tables from baseline to highest/lowest post-baseline value in the treatment period will be based on laboratory ranges. The laboratory ranges are defined for fasting values.

Shift tables for eosinophil values from baseline to end of treatment period and to highest/lowest post-baseline value in the treatment period will be summarised in the following categories: $\leq 0.5 \cdot 10^9$/L, $>0.5 \cdot 10^9$/L to $\leq 1.5 \cdot 10^9$/L, and $>1.5 \cdot 10^9$/L.

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

Table 3: 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	< 1.0×10^9/L, < 0.5×10^9/L	> 5.0×10^9/L
Monocytes, absolute count	10^9/L	< 0.1×10^9/L	> 0.8×10^9/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	< 100×10^9/L, < 30×10^9/L, < 10×10^9/L	> 450×10^9/L

Abbreviations: HDL = high density lipoprotein; LDL = low density lipoprotein; N/A = not applicable; 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.

6.7.6 Pharmacokinetics and anti-drug antibodies

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

6.8 General Principles

In addition to what is stated in the protocol, the lower and upper quartiles will be used to summarise continuous data.

6.8.1 Baseline value

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

Missing baseline assessments

When the baseline value is missing, endpoints concerning a change from baseline cannot 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.

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

Date of permanent discontinuation of IMP

Defined for subjects who have a reason for permanent discontinuation of IMP recorded.

Defined as the latest of date of early termination visit (if existing) or date of onset of latest AE leading to withdrawal of trial product, otherwise date of the last visit, excluding safety follow-up and nominal Week 16 visits.

Exposure start

Date and time of first dose.

Exposure end

Date of Week 16 visit (if existing) at time 23:59:00, otherwise date of permanent discontinuation of IMP (if existing) at time 23:59:00, otherwise date of last IMP administration at time 23:59:00.

Date of last contact

Date of very last contact found by examining all time and date information in eCRF, laboratory, ECG, and PRO.

Trial periods

The time from exposure start to exposure end will be assigned to the treatment period and remaining time after exposure end will be assigned to the safety follow-up period as shown in Table 4 (ADaM variable APHASE). The ADaM variable APERIODC will indicate the latest treatment 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)
Treatment period	Exposure start	Exposure end
Safety follow-up period[1]	First day after exposure end	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)
Treatment period	Exposure start	Date of last contact at time 23:59:00

6.8.3 Incomplete dates

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 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 treatment or safety 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 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 treatment or safety 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 are not missing, it will be assumed that the start day is the first day of the month. If the medication start day and month are 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 are missing, it will be assumed that the medication was started before trial 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 are not missing, it will be assumed that the end day is the last day of the month. If the medication end day and month are 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 are missing, it will be assumed that the medication was ongoing at the end of the trial, and the date will appear as missing in the data.

Administration of IMP

In case of incomplete time registrations of IMP dosing with dates of administration being available, the time of 12:00:00 will be used.

6.8.4 Conventions regarding time of day for concomitant medication

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 and trial completers

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

Trial completers will be defined as stated in the protocol. Reason for not completing the trial will be assessed using the alternatives listed for not attending the safety follow-up visit except for the alternatives ‘transferred to 1337’ and ‘safety follow-up information collected at nominal Week 16 visit’.

6.8.6 Early termination and unscheduled visits

When no data are available from a certain scheduled post-baseline visit for a subject, data from early termination visits and unscheduled visits have the potential to replace data from that particular scheduled visit in data summaries, provided the data are collected between 6 days before and 7 days after the planned time point for the scheduled 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, ..., 16)	Day 7*x-6 to 7*x+7
Safety follow-up	36-49 days after last dose[1] 106-119 days after first dose[2]

1) Subjects who permanently discontinues IMP dosing with last IMP administration <5 weeks before the planned Week 16 visit or complete the treatment period, should have the safety follow-up visit conducted 6 weeks after the last IMP administration.

2) If a subject permanently discontinues IMP dosing with last IMP administration ≥5 weeks before the planned Week 16 visit, then only the nominal Week 16 visit (16 weeks after randomisation) will be conducted. At this visit, the relevant safety information will be collected.

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 visit and several unscheduled visits exist within the window, 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 dropouts and missing values

Intercurrent events and missing values will be handled as described in the clinical trial protocol.

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
Treatment period	Tralokinumab + TCS	Tralokinumab Q2W + TCS	1
Treatment period	Placebo + TCS	Placebo + TCS	2

6.8.9 Protocol deviations

Only major protocol deviations will be summarised and listed.

7 References

1. White IR, Daniel R, Royston P. Avoiding bias due to perfect prediction in multiple imputation of incomplete categorical variables. Computational Statistics and Data Analysis 54 (2010): 2267-2275.

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