Dermatology beyond the skin

Cover Page

Official title: A randomised, double blind, placebo controlled trial to evaluate the effect of tralokinumab on vaccine antibody responses in adults with moderate-to-severe atopic dermatitis who are candidates for systemic therapy
LEO Pharma number: LP0162-1341
NCT number: NCT03562377
Date: 18-Oct-2019

Statistical analysis plan

Vaccine responses in tralokinumab-treated atopic dermatitis

ECZTRA 5 (ECZema TRAlokinumab trial no. 5)

Phase 2 – Vaccine response trial

A randomised, double-blind, placebo-controlled trial to evaluate the effect of tralokinumab on vaccine antibody responses in adults with moderate-to-severe atopic dermatitis who are candidates for systemic therapy

LEO Pharma A/S	**Trial ID:**	**LP0162-1341**
	Date:	**18-OCT-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, Medical Sciences

PPD

Medical Lead, Medical Sciences

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

AD	atopic dermatitis
ADA	anti-drug antibodies
ADaM	analysis data model
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BSA	body surface area
CI	Confidence interval
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 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)
IgG	immunoglobulin G immunoglobulin G
IMP	investigational medicinal product
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
nAB	neutralising antibodies
POEM	Patient-Oriented Eczema Measure
PYE	patient years of exposure
Q2W	every 2 weeks
QC	quality control
SAE	serious adverse event
SCORAD	Scoring Atopic Dermatitis
SCORAD50	At least 50% reduction in SCORAD score
SCORAD75	At least 75% reduction in SCORAD score
SOC	system organ class

Tdap	Tetanus, diphtheria and acellular pertussis
ULN	upper limit of normal
VAS	visual analogue scale

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.

Definition of vaccine response:

1. The definition and calculation of positive meningococcal response has been specified.

New analysis for the continuous other endpoints:

2. Analysis of a new tertiary estimand (‘composite’) for the continuous other endpoint ‘Change from baseline to Week 16 in EASI score’ is introduced. Analysis apply non-responder imputation for subjects who receive rescue medication.

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

The per protocol analysis set:

4. The definition of the per protocol analysis set as stated in the protocol has been updated with regards to handling of systemic rescue medication, baseline disease severity related to the EASI status and visit interval between administration of the vaccine and measurement of the vaccine response.

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 randomised to treatment who were exposed to IMP (tralokinumab/placebo) are included in the full analysis set and will be analysed for efficacy up to Week 16 (Visit 11). For subjects not exposed to IMP (tralokinumab/placebo), the decision to withdraw can't be biased by knowledge of the assigned treatment due to the blinding. This definition of the full analysis set 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 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.

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 6.9.2 for further details.

For analysis of efficacy, subjects will be included 'as randomised'.

For analysis of safety, if a subject is mistakenly given an IMP other than that to which they were randomised, they will be analysed '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 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 definition of the per protocol analysis set as described in the protocol has been updated to accept negligible deviations in baseline disease severity related to the EASI status. Thus, the criteria from inclusion criterion 7 have been modified to require an EASI score of ≥12 at screening OR ≥16 at baseline instead of requiring both criteria to be met. The rationale for this change is that marginal deviations in baseline disease severity is not considered to affect the vaccine response.

The criteria related to systemic rescue medication in the definition of the per protocol analysis set have been updated relative to the protocol text to include, not only those for the AD indication but all systemic immunosuppressive treatments irrespectively of indication. The referred criteria for excluding patients consequently become:

- Initiated systemic immunosuppressive treatment prior to Week 10 and who are still treated with or exposed to the given treatment at Week 10 (that is, Week 10 [visit 8] occurs within 5 half-lives after the last dose of the given systemic immunosuppressive medication).
- Initiated systemic immunosuppressive treatment at any time point from Week 10 to Week 16.

The rationale for excluding these subjects is to ensure that subjects were not immunosuppressed by these treatments when the vaccinations were administered, as this might impact the response to the vaccination, and thereby the primary endpoints. This is independent of the indication for the immunosuppressive treatments and should therefore include all subjects treated with systemic immunosuppressants, irrespectively of the indication.

In addition to the criteria specified in the protocol, subjects with Week 16 visit occurring ≥56 days after the Week 12 visit, are not included in per protocol analysis set due to a too long interval between administration of the vaccine and measurement of the vaccine response, since this would induce a risk of a perished vaccine response.

Systemic immunosuppressive treatment definition

ATC2 code H02 or L04 will be used to identify administered systemic immunosuppressive treatments. Table 1 below presents the medications that as minimum will be identified in the trial (as being systemic immunosuppressive) along with the half-lives applied to evaluate the PP exclusion criteria.

Medications administered in the screening period will be included in the search to ensure that all administered medications that could potentially be immunosuppressive at time of vaccination will be covered. Different routes of administration can be used for the medications, which will result in different half-lives.

Table 1: Systemic immunosuppressive treatments and applied halflives

ATC 4	ATC 4 TERM	Standardized Medication Name	Route of Administration	Halflife		
				Hours	Weeks	5 x $t_{½}$[1]
H02AB	GLUCOCORTICOIDS	DEXAMETHASONE	ORAL	7.2	0.0	0.2

H02AB	GLUCOCORTICOIDS	DEXAMETHASONE SODIUM PHOSPHATE	INTRAVENOUS	24	0.1	0.7
H02AB	GLUCOCORTICOIDS	DEXAMETHASONE SODIUM PHOSPHATE	SUBCUTANEOUS	336	2.0	10.0
H02AB	GLUCOCORTICOIDS	HYDROCORTISONE SODIUM SUCCINATE	INTRAVENOUS	3	0.0	0.1
H02AB	GLUCOCORTICOIDS	METHYLPREDNISOLONE	ORAL	3.5	0.0	0.1
H02AB	GLUCOCORTICOIDS	METHYLPREDNISOLONE SODIUM SUCCINATE	INTRAVENOUS	24	0.1	0.7
H02AB	GLUCOCORTICOIDS	PREDNISONE	ORAL	3	0.0	0.1
H02AB	GLUCOCORTICOIDS	TRIAMCINOLONE ACETONIDE[2]	INTRAMUSCULAR	336	2.0	10.0
H02AA	MINERALOCORTICOIDS	FLUDROCORTISONE ACETATE	ORAL	0.5	0.0	0.0
L04AC	INTERLEUKIN INHIBITORS	DUPILUMAB	SUBCUTANEOUS	432	2.6	12.9
L04AC	INTERLEUKIN INHIBITORS	DUPILUMAB	INTRAMUSCULAR	432	2.6	12.9
L04AC	INTERLEUKIN INHIBITORS	NEMOLIZUMAB	SUBCUTANEOUS	432	2.6	12.9
L04AX	OTHER IMMUNOSUPPRESSANTS	AZATHIOPRINE	ORAL	5	0.1	0.1
L04AX	OTHER IMMUNOSUPPRESSANTS	METHOTREXATE	ORAL	15	0.1	0.4
L04AA	SELECTIVE IMMUNOSUPPRESSANTS	BARICITINIB	ORAL	12.5	0.1	0.4
L04AA	SELECTIVE IMMUNOSUPPRESSANTS	MYCOPHENOLATE SODIUM	ORAL	17	0.1	0.5

[1] 5 times the halflife (t½) is presented in weeks.

[2] Intralaminar and intraarticular administration of Triamcinolone Acetonide is not considered systemic treatment

Systemic immunosuppressive medications were prohibited during the trial, and wash-out criteria were specified in the exclusion criteria of the protocol accordingly. For completeness, medications that required wash-out will be included in the above search.

6 Statistical analysis

6.1 Baseline characteristics

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. For further details, see Section 6.9.3.

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.

The table of rescue medication will include medications taken after the first dose and before the Week 16 visit (or before day 7*16=112 after first dose, in case the Week 16 visit did not take place).

Rescue medication will be summarised for the treatment 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.

6.4 Compliance

Compliance will be summarised and listed.

6.5 Exposure

The exposure time will be defined as detailed in Section 6.9.2. 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.

6.6 Vaccine responders

As stated in the protocol, a positive anti-tetanus response is defined as a 3-fold IgG increase at Week 16 compared to Week 12 if IgG ≤1.0 IU/mL at Week 12; or IgG ≥2.5 IU/mL if IgG >1.0 IU/mL at Week 12.

As stated in the protocol, a positive anti-meningococcal response is defined as at least a 3-fold increase in specific IgG at Week 16 compared to Week 12.

The anti-meningococcal response is measured in separate assays against four individual meningococcal serogroup antigens, including serogroup A, C, W-135 and Y. To assess the vaccine response against a serogroup antigen a measurable specific IgG titer against that antigen at both week 12 and week 16 should be available. Subjects with a visit interval between Week 12 and Week 16 of ≥56 days are excluded from the analysis due to a too long interval between administration of the vaccine and measurement of the vaccine response.

In order to reduce the impact of missing data on the calculation of responders to the meningococcal vaccination the following will be applied:

- If data are available for 4 out of the four antigens, then the subject should be a responder against at least 3 of the antigens
- If data are only available for 3 out of the four antigens, then the subject should be a responder against these 3 antigens
- If data are only available for 2 out of the four antigens, then the subject should be a responder against these 2 antigens
- If data are only available for 1 out of the four antigens, then the subject should be a responder against this 1 antigen

6.7 Analysis of efficacy

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

Sensitivity analysis 2 for the primary estimand (secondary 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.

Primary analysis of primary estimand (continuous other endpoints)

It is specified in the protocol that the continuous other 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.

Tertiary (composite) estimand (continuous other endpoints)

For the continuous other endpoint 'Change from baseline to Week 16 in EASI score' 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 other endpoints. Thus, a new tertiary 'Composite' estimand for the continuous other endpoints is introduced.

Primary analysis for the tertiary (composite) estimand (continuous other 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=11109941) 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 other endpoint will be analysed using an ANCOVA model with effects of treatment, 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.

Multiple imputation

For the analysis of the 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 11109941 will be used. The remaining seeds are specified in the protocol.

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 2.

Table 2: 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)

For the analysis of binary efficacy endpoints, it may for the tertiary (treatment policy) estimand not be possible to conduct a multiple imputation procedure if too few subjects have retrieved data, e.g. at Week 16. In such cases, the analysis may be omitted.

Percentage change in EASI score

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

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 at Week 16 by baseline IGA

- EASI75 at Week 16 by baseline IGA

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 1 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 1 question is missing within a subscale, the subscale is considered missing.

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 Analysis of safety

6.8.1 Adverse events

AEs will be summarised and listed.

Assignment of AEs to periods

An 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 6.9.2, Table 6).

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 6.9.2) will be assigned to the safety follow-up treatment period.

For handling of incomplete start dates of AEs, see Section 6.9.3.

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 in the Tralokinumab group.

Other adverse events

A MedDRA search on all reported AEs was specified to capture AEs belonging to injection site reactions. The MedDRA search to capture this safety area of interest was performed using the following HLGT levels (based on primary and secondary terms): 'administration site reactions NEC', 'application and instillation site reactions', and 'injection site reactions.

6.8.2 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.

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

Table 3: 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

Abbrevations: PCS=potentially clinically significant.

6.8.3 Electrocardiogram

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

6.8.4 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 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 4.

Table 4: 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).

6.8.5 Urinalysis

Urinalysis data will be summarised and listed.

Potentially clinically significant values will be defined as displayed in Table 5.

Table 5: 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

Abbreviations: ACM = ACM Global Laboratories; HPF = high power field; LPF = low power field; N/A = not applicable; PCS = potentially clinically significant; RBC = red blood cells; ULN = upper limit of normal (i.e., upper limit of normal reference range); WBC = white blood cells.

6.8.6 Pharmacokinetics and anti-drug antibodies

Pharmacokinetics and ADA data will be summarised and listed.

The ADA status will be categorised as follows:

- Positive
    1. Pre-existing: ADA-positive at baseline, no post-baseline ADA response ≥ 4-fold over baseline titre level, and at least 1 non-missing post-baseline ADA assessment.
    2. Treatment-boosted: ADA-positive at baseline and at least 1 post-baseline ADA response ≥ 4-fold over baseline titre level.
    3. Treatment-emergent: ADA negative or missing at baseline and at least 1 positive post-baseline ADA response.
- Negative
    1. ADA negative or missing at baseline, all post-baseline ADA assessments negative.
- No post-baseline ADA assessment.

6.9 General principles

6.9.1 Baseline value

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

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

Date of permanent discontinuation of IMP (tralokinumab/placebo)
Defined for subjects who have a reason for permanent discontinuation of IMP (tralokinumab/placebo) 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 (tralokinumab/placebo) at time 23:59:00.

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 6 (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 7).

Table 6: 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]	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 7: 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

6.9.3 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 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.

6.9.4 Early termination and unscheduled visits

When no data are 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 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	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 visit 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.

6.9.5 Handling of drop-outs and missing values

Missing values will be handled as described in the clinical trial protocol.

Week 16 last observation carried forward

As specified in the protocol, a sensitivity analysis of the secondary endpoints 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.

6.9.6 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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