Cover Page

Official title: A randomised, double-blind, placebo-controlled, parallel-group, multi-centre, phase 3 trial investigating the efficacy, safety, and tolerability of tralokinumab administered in combination with topical corticosteroids to adult subjects with severe atopic dermatitis who are not adequately controlled with or have contraindications to oral cyclosporine A
LEO Pharma number: LP0162-1346
NCT number: NCT03761537
Date: 21-Oct-2020

Statistical Analysis Plan

LP0162-1346

Tralokinumab in combination with topical corticosteroids in subjects with severe atopic dermatitis who are not adequately controlled with or have contraindications to oral cyclosporine A

ECZTRA 7 (ECZema TRAlokinumab trial no. 7)

Phase 3 – efficacy and safety trial

A randomised, double-blind, placebo-controlled, parallel-group, multi-centre, phase 3 trial investigating the efficacy, safety, and tolerability of tralokinumab administered in combination with topical corticosteroids to adult subjects with severe atopic dermatitis who are not adequately controlled with or have contraindications to oral cyclosporine A

LEO Pharma A/S	**Trial ID:**	**LP0162-1346**
	Date:	**21-OCT-2020**
	Version:	**v1.0**

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 Stat

Biostatistics Lead, Medical Sciences

PPD , MD

Medical Lead, Medical Sciences

PPD , MSc Stat

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
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CSA	Cyclosporine A
CTR	Clinical trial report
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
FAS	Full analysis set
FDA	US. Food and Drug Administration
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator's Global Assessment
IMP	Investigational medicinal product
LOCF	Last observation carried forward
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation

nAB	Neutralising antibodies
NRS	Numeric rating scale
POEM	Patient Oriented Eczema Measure
PT	Preferred term
Q2W	Every 2 weeks
QC	Quality control
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SCORAD	Scoring Atopic Dermatitis
SF-36	36-Item Short Form Health Survey
TCS	Topical corticosteroid
SOC	System Organ Class
VAS	Visual analogue scale

4 Introduction

The statistical analysis will be performed as outlined in the Clinical Trial Protocol. This Statistical Analysis Plan (SAP), prepared before the unblinding of the trial, contains a more technical and detailed elaboration of relevant points in the statistical analysis described in the Clinical Trial Protocol.

Change log of major changes or additions to the protocol, made in this SAP:

1. Major eligibility criteria have been defined and a review of all critical protocol deviations has been formalised in accordance with ICH E9 and the protocol. From these, it will be possible to make exclusions to the full analysis set during a blind review of data.
2. Further specification to the analyses of the primary and secondary endpoints, where applicable, in relation to when there is not enough data to facilitate MI of data using Rubin's rule and the handling of such situations.

5 Trial analysis sets

As specified in the protocol, but with some further specification of the full analysis set (FAS).

The FAS will, as specified in protocol, consist of all subjects randomised and dosed with IMP. But, in addition to this, exclusions can be made in accordance ICH E9 if major eligibility criteria have been breached or a critical protocol deviation has been identified to seriously impact data integrity in relation to the primary endpoint of this trial. These major eligibility criteria are inclusion criteria 3, 6, 7, 8, and 12, as defined in the protocol. These are selected due to their criticality in relation to defining the targeted population.

During the blind review of data each critical protocol deviation and any violation of the defined major eligibility criteria will be reviewed, and a decision will be made whether the subject will be removed from or kept in the FAS.

In the analysis set definition document, made prior to unblinding of the trial, documentation of any exclusions will be made and each critical protocol deviation will have a reason for excluding or not excluding the subject from the FAS.

6 Statistical analysis

6.1 Aspects related to the COVID-19 pandemic

As specified in the protocol. Technical aspects of attributing events and missing data to the COVID-19 pandemic is further detailed in Section 6.8.8.

6.2 Disposition

Subject disposition will be summarised as detailed in the protocol.

Additionally, reasons for not attending the nominal Week 16 and Week 26 visits will be summarised for randomised subjects. Not attending the nominal Week 16 and Week 26 visits due to the COVID-19 pandemic will be added to the list of reasons based on the information documented in the eCRF. Technical aspects of attributing missed visits to the COVID-19 pandemic is further detailed in Section 6.8.8.

The number of randomised subjects and screen failures will be summarised for all screened subjects. Screen failures will be summarised by reason as well as overall.

For the safety follow-up visit, attendance will be summarised for all subjects included in the safety follow-up analysis set. Not attending the safety follow-up visit due to the COVID-19

pandemic will be added to the list of reasons, as for reasons for not attending the nominal Week 16 and Week 26 visits.

6.3 Demographics and baseline characteristics

Demographics and baseline characteristics will be summarised as specified in the protocol.

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 with start date before or at the Week 0 visit date which does not have an end date before the Week 0 visit date. For handling of incomplete dates, see Section 6.8.3.

In addition, any concomitant medication taken during the treatment period will be summarised.

In case a subject has been randomised based on a wrong value of a stratification variable, the correct value of the variable will always be used in descriptive statistics and analyses. Subject(s) who were randomised within a wrong stratum will be listed.

6.4 Exposure and treatment compliance

6.4.1 Compliance

Compliance will be summarised and listed. Technical aspects of attributing missed IMP doses to the COVID-19 pandemic are further detailed in Section 6.8.8.

6.4.2 Exposure

Exposure time will be summarised as detailed in the protocol with the exception that it will be presented using years of exposure instead of days. Definitions used for exposure time during the treatment period is detailed in Section 6.8.2.

6.5 Rescue treatment

Presentation of rescue treatment and the definition of rescue treatment is as defined in the protocol.

For the presentation of rescue treatment up until the Week 16 visit (actual or nominal) the planned date of the Week 16 visit will be used if no Week 16 visit exists (actual or nominal).

Due to the allowance of TCS in the screening period, some subjects might during this period use TCS of a high enough potency to be categorised as rescue treatment ending on the day of randomisation. Such cases will not be categorised as rescue medication as the assumption will be that the use of high potency TCS will stop prior to administration of IMP.

The global start date of the COVID-19 pandemic is defined in Section 6.8.2.

6.6 Analysis of efficacy

As described in Section 6.3, in case a subject is randomised based on a wrong value of a stratification variable, the correct value of the variable will always be used in the analysis to reflect the actual characteristics of the subject. The variable collected at randomisation will be used.

6.6.1 Intercurrent events

As specified in the protocol. The timing and technical handling of intercurrent events in relation to analysed visits and the technical aspects of attributing events and missing data to the COVID-19 pandemic are further detailed in Sections 6.8.5, 6.8.6 and 6.8.8.

6.6.2 Analysis of the primary endpoint (EASI75 at week 16)

The analysis of the primary endpoint will be as specified in the protocol, further changes or specifications to the analysis of the endpoint are described here.

Primary analysis of the primary estimand ('COVID-19 modified composite')

In case not enough data is missing due to the COVID-19 pandemic or set to missing due to subject-onset of the COVID-19 pandemic (less than 2 imputed values within treatment groups), the primary analysis of the secondary estimand (composite) will be used instead, as it will not be possible to estimate the variance using Rubin's rule for MI.

Primary analysis of the tertiary estimand ('treatment policy')

As stated in the protocol, it is expected that the number of observed values in the 2 treatment groups of discontinued subjects is too small to facilitate MI of data using Rubin's rule. In this case, the primary analysis will be substituted with the sensitivity analysis. A limit of 2 or less observed values within each of the treatment groups of discontinued subjects will be used to enforce when the sensitivity analysis will become the primary analysis.

Sensitivity analysis of the tertiary estimand ('treatment policy')

For the 2 treatment groups within the discontinued subjects, in case not enough data (less than 2 data points) is missing due to the COVID-19 pandemic or set to missing due to subject-onset of the COVID-19 pandemic, the sensitivity analysis will assume any missing data to be non-response, as it will not be possible to estimate the variance using Rubin's rule for MI.

6.6.3 Analysis of secondary endpoints

6.6.3.1 Binary secondary endpoints

The analysis of the binary secondary endpoints will be as specified in the protocol and section 6.6.2, further changes or specifications for endpoints' analyses are described here.

Multiple imputation is further specified in section 6.6.4.

Calculation of Weekly average of Worst Daily pruritus NRS

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

The baseline value of the Worst Daily Pruritus NRS (weekly average) will be calculated as defined in the protocol based on daily assessments of the 7 days preceding randomisation including day of randomisation (day -6 to 0 where day 0 is the day of randomisation).

For the treatment period, the Worst Daily Pruritus 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 week 2 to week 25, 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).

Since the Week 26 visit (regular or nominal) may occur between day 179 and day 185, the week 26 weekly average will instead be based on the 7 days before (and including) the day of the week 26 visit (regular or nominal). In case no week 26 visit (regular or nominal) exists, the date of an unscheduled visit or early termination visit can be mapped as per Section 6.8.4 (if existing), else the planned date will be used.

Sensitivity analyses of the primary estimand of IGA 0/1 and reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 at Week 16 and 26

The tipping-point analyses are not considered relevant for secondary endpoints, thus the sensitivity analyses of the primary estimand of IGA 0/1 and reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 at Weeks 16 and 26 will not be done.

Subgroup analyses

During the analysis of blinded data, possible convergence issues of the conditional logistic regression have been discovered for individual imputation datasets, but not all imputation

datasets at once. This might not happen when the trial is unblinded, but in the event that it does, the analysis methods for the test of interaction can be re-opened for individual subgroup analyses if this issue is discovered. If this were to occur on unblinded data, the first step will be to relax the convergence criterion from the standard of $1 * 10^{-8}$ to $1 * 10^{-6}$. If other measures are needed, it will be documented in the clinical trial report.

6.6.3.2 Continuous secondary endpoints

Primary analysis of primary continuous estimand ('hypothetical')

Some subjects may not have any post-baseline data collected before initiation of rescue medication, have permanently discontinued IMP, or having subject-onset of the COVID-19 pandemic prior to the first post-baseline assessment. To ensure that all eligible subjects are included in the analysis, the baseline value will be carried forward as the first post-baseline assessment for these subjects, corresponding to imputing a change of 0 at the first post-baseline assessment. Additionally, subjects might be early terminated from the trial prior to the first scheduled post-baseline assessment with an assessment being done at the early termination visit. In this case the last assessment (including the baseline assessment) done prior to the first scheduled post-baseline assessment will be carried forward to the first scheduled post-baseline assessment.

Primary analysis of the secondary continuous estimand ('treatment policy')

Due to the high chance of discontinued subjects opting not to attend the nominal Week 16 / 26 visits, a general conservative rule is put in place. In case within one of the 4 groups defined is 2 or less observed values the missing data will be imputed using the worst observation carried forward.

In the multiple imputation methods specified, the variables used in the imputation procedures will not be prior CSA use and baseline IGA, but prior CSA use, county (Germany Yes/No), and baseline IGA.

Sensitivity analysis of the secondary continuous estimand ('treatment policy')

As for the primary analysis of this estimand, the sensitivity analysis will also have the general rule applied if there are not enough observed data to facilitate MI of data. Since the MI in this sensitivity analysis applies a copy-reference approach, only the discontinued/non-discontinued subjects randomised to placebo are applicable for this. The rule will, again, be that if there are 2 or less observed values at the analysed visit in the respective placebo group

then missing data within the group will be imputed using the worst observation carried forward.

In the multiple imputation methods specified, the variables used in the imputation procedures will not be prior CSA use and baseline IGA, but prior CSA use, county (Germany Yes/No), and baseline IGA.

Primary analysis of the tertiary estimand (COVID-19 modified composite)

In the multiple imputation methods specified, the variables used in the imputation procedures will not be prior CSA use and baseline IGA, but prior CSA use, county (Germany Yes/No), and baseline IGA.

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 of 100% then there is no area to score. In the event that dryness is missing and extent is 100% then 0 (none/absent) will be imputed instead.

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. Unless otherwise specified in the protocol or this SAP, the seed 11109946 will be used in any multiple imputation strategies.

When performing multiple imputation of continuous parameter values, imputed values outside the relevant parameter scale for visits prior to the relevant visit will be used as it is. Values imputed at the relevant visit will be truncated to the nearest upper or lower bound on the given scale. E.g., negative imputed EASI values at Week 16 will be set to 0 in an analysis of Week 16 data.

Secondary endpoints IGA 0/1

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. Imputation will be performed within treatment groups at each visit. E.g. if at a visit within one treatment group, the IGA values (0,1,2,3) for each level have 2 or more observed values but the IGA value of 4 only has 1 or less, the imputation model will not be able to predict for IGA

values of 4 at that specific visit. I.e. categories can be combined at a visit for one group, but not the other. To avoid this situation, in this specific example IGA values of 3 and 4 will be combined into a single category prior to 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 imputation, according to the rules in Table 1.

Table 1: Adjacent IGA categories combined if a predictor contains 1 or less observed values

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

6.6.5 Analysis of other endpoints

As specified in the protocol, but with the change that 'Other' endpoints will not be analysed for the secondary estimand ('composite'), but for the tertiary estimand ('treatment policy'), as originally proposed in previous versions of the protocol.

Percent change of DLQI

The analyses of percent change in DLQI at Week 16 and Week 26 have been added in support of the secondary endpoints.

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.

HADS

For the analysis of the endpoint HADS-anxiety < 8 and HADS-depression < 8, the imputation of missing data due to the COVID-19 pandemic or set to missing due to the COVID-19

pandemic will be imputed within each sub-score prior to analysis using the primary analysis of the primary estimand.

Amount of TCS used

The amount of TCS used will be calculated as specified in section 6.6.8 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.

In an extra sensitivity analysis, the amount of TCS used will be log transformed. This transformation has in a similar trial proven to fit data better. TCS amount will be log transformed by adding 1 (due to potential zero values) and then taking the logarithm. The analysis will use the same repeated measures model with the mean modelled as follows:

log[TCS amount used + 1] (g) = Treatment*visit + prior CSA use + country + Baseline IGA

The analysis results will be presented by back-transforming using the exponential function, thus producing estimated geometric means and estimated ratio of means, which will be presented with nominal p-values and 95% confidence intervals (CI). This sensitivity analysis will be done for both consumption assumptions.

Additionally, descriptive histograms of both consumption assumptions will be produced for the amount of TCS.

Number of days without topical treatment use

The number of days without topical treatment use will be analysed 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).

Scoring of PROs

Table 2: 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	Version 2, acute recall.

6.6.6 Analysis of patient-reported outcomes

As specified in the protocol.

6.6.7 Analysis of exploratory supporting endpoints

As specified in the protocol.

6.6.8 Drug 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.

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

- If tubes are returned at the wrong visit, the amount of TCS used from these tubes will be assumed to be used in the period from the tubes being dispensed to being returned.
- 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, conservatively, 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 dispensed tubes have no weighing data due to any other cause the most conservative estimate will be imputed, i.e. that the whole tube dispensed was used.

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). If all tubes in the batch are not dispensed/returned at the same time, date of the first dispensed or last returned tube in the batch is used, dependent on the situation. The amount of the 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.

6.6.9 Descriptive statistics

In support of all endpoints, summaries will be included for all observed scores by visit.

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 (AEs) will be summarised and listed. However, the summaries will be split into the two periods, the treatment period and the safety follow-up period. This is to differentiate the AEs based on whether or not subjects are on active treatment.

The start date of the COVID-19 pandemic is defined in Section 6.8.2.

Assignment of AEs to periods

An AE will be assigned to a given period (treatment or safety follow-up) if the start date of the AE is after the start date and before or at the end date of that period (see Section 6.8.2, 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.

For the 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 be sorted by decreasing number of affected subjects:

- For the treatment period, AE tables will be sorted by decreasing number of affected subjects in the Tralokinumab Q2W+TCS group. AEs only occurring in the Placebo+TCS group will be sorted last by decreasing number of affected subjects in the Placebo+TCS group.

- For the safety follow-up period, AE tables will be sorted by decreasing total (whole trial period) number of affected subjects in the Tralokinumab Q2W+TCS group. AEs only occurring in the Placebo+TCS group will be sorted last by decreasing number of affected subjects in the Placebo+TCS group.

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 every 30 minutes or until stable, these measurements will be listed.

6.7.3 ECG

ECG data will be summarised and listed for the treatment period. ECG data from the safety follow-up period will be listed.

The overall central evaluation of ECG will be presented using shift tables for the treatment period.

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.

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

Protocol Lab parameter	**SI Unit**	**PCS low**	**PCS High**
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 presented as detailed in the protocol under ‘Clinical laboratory evaluation’, Section 14.3.9.3.

Potentially clinically significant values will be defined as displayed in Table 4.

Table 4: Potentially clinically significant urinalysis values

Protocol lab parameter (Central lab parameter)	SI Unit	PCS low	PCS High
Erythrocytes	/HPF	N/A	> 3, >10, >25, >50
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;

6.7.6 Pharmacokinetics and anti-drug antibodies

Pharmacokinetics and anti-drug antibodies data will be summarised as detailed in the protocol, but for the treatment period only.

An extra summarisation will be made over ADA status across the entire trial.

6.8 General Principles

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 is unrelated to the assigned treatment, bias should not be a concern with this approach.

6.8.2 Definition of trial periods, date of permanent discontinuation of IMP and start of the COVID-19 pandemic

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

The latest date of either is the date of permanent discontinuation of IMP: The date of early termination visit (if existing) or the date of onset of latest AE leading to withdrawal of IMP (if existing). Otherwise, the date of the last visit, excluding safety follow-up, nominal Week 16 visit and nominal Week 26 visit, unless the last visit is the Week 26 visit in which case the subsequent scheduled visit following the last administered IMP dose will be used (observed date (if existing) else planned date + 7 days).

Unscheduled visits can be used as the date of permanent discontinuation of IMP if the unscheduled visit is within the window for where subjects can be dosed. This means that only unscheduled visits between the baseline visit and the Week 24 visit (if existing), or the planned visit + 7 days will be used to account for the visit window.

Exposure start
Date and time of first dose.

Exposure end
Date of Week 26 visit (if existing) at time 23:59:50, otherwise date of permanent discontinuation of IMP (if existing) at time 23:59:50, 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, PRO and eDiary data.

Start of the COVID-19 pandemic

The start of the COVID-19 pandemic will be set to the 1st of March 2020 at time 00:00:00 across the whole trial. The date was decided based on the fact that at this date the trial procedures were most likely not impacted by the COVID-19 pandemic but still keeping it as close as possible to the first observed occurrence of missed procedures due to the COVID-19 pandemic.

Trial periods

For efficacy assessments the analysis set are defined only for the treatment period which is listed in Table 5 (ADaM variable APERIOD).

For safety assessments, the two analysis sets are defined by a start and end of each period which are listed in Table 6 (ADaM variable APHASE).

Additionally, a sub-trial period is defined for the safety assessments considering the COVID-19 pandemic. For this we define the start and stop for the treatment and safety follow-up periods prior to and after the start of the COVID-19 pandemic which are listed in Table 7.

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

APERIOD	**Start of period**	**End of period (only if start date exists)**
Treatment period	Exposure start	Date of last contact at time 23:59:59

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	Exposure end (plus 1 second)	Date of safety follow-up visit (if existing) at time 23:59:59 else

		Date of last contact at time 23:59:59

Table 7: Start and end time of trial periods related to onset of the COVID-19 pandemic

	Start of period	**End of period (only if start date exists)**
Treatment period, prior to the start of the COVID-19 pandemic	Exposure start if prior to the start of the COVID-19 pandemic else Missing	Whichever comes first of: Exposure end or Start of the COVID-19 pandemic
Treatment period, after the start of the COVID-19 pandemic	Start of the COVID-19 pandemic if between exposure start and exposure end else Exposure start if after the start of the COVID-19 pandemic else Missing	Exposure end if after the start of the COVID-19 pandemic else Missing
Safety follow-up period, prior to the start of the COVID-19 pandemic	Exposure end (plus 1 second) if prior to the start of the COVID-19 pandemic else Missing	Whichever comes first of: Date of safety follow-up visit (if existing) at time 23:59:59 else Date of last contact at time 23:59:59 or Start of the COVID-19 pandemic
Safety follow-up period, after the start of the COVID-19 pandemic	Start of the COVID-19 pandemic if between Exposure end (plus 1 second), and Date of safety follow-up visit (if existing) at time 23:59:59 else Date of last contact at time 23:59:59 else Missing	Date of safety follow-up visit (if existing) at time 23:59:59 else Date of last contact at time 23:59:59, if after the start of the COVID-19 pandemic else Missing

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 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 and year is not missing and before the month of the exposure start and before or at the year of 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 and year is not missing and before the month of the exposure start and before or at the year 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 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. Time of medication will be set to 23:59:59.

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. Time of medication will be set to 00:00:00, unless the end date is equal to the start date of the concomitant medication where the time of the end date will be set to 23:59:59.

Administration of IMP

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

6.8.4 Early termination and unscheduled visits

When no data is 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 that the data is collected between 6 days before and 7 days after the planned time point for the scheduled visit, as displayed below.

Table 8: Visit days and windows

Visit (Target day)	Visit window (Day is date of assessment minus date of first dose)
Week 2 (Day 14)	Day 8 to 21
Week x (Day 7*x) (where x= 4, 6, ..., 26)	Day 7*x-6 to 7*x+7
Safety follow-up	106-119 days after last dose

When data from both unscheduled and early termination visits exist within the given visit window, the early termination visit will be selected for analysis. When no data from early termination visit and data from unscheduled visit(s) exist, within window, the unscheduled visit will be selected for analysis. If several unscheduled visits exist, the one closest to the target day will be selected for analysis. If the distance to the target day is tied, the latest unscheduled visit will be selected.

6.8.5 Technical handling of intercurrent events and missing values

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

This section describes the technical aspects in relation to this.

The variable DTYPE is created to indicate each special handling of data used. Observed data will be indicated when DTYPE is empty (DTYPE=''). Subjects having experienced a prior intercurrent event or having a missing value at a visit can have inserted 5 extra data rows of separate DTYPEs. These data rows will be inserted dependent on the needs of the estimands applied. Non-responder imputation will be indicated using DTYPE='NRI', no value will be imputed but criteria/outcome values will be imputed as non-response. Worst observation carried forward will be indicated using DTYPE='WOCF', imputing the worst observation observed up until and including the data point. When imputing values, DTYPE='MISSING' will be used on relevant missing or set to missing data. In addition, to indicate when there is no observed value an extra category DTYPE='MISSOBS' is created. DTYPE='LOCF', last observation carried forward (including baseline observation) is used in the special case when no assessments exist at the first scheduled post-baseline assessment visit prior to any intercurrent events.

As intercurrent events are handled based on whichever of the regarded prior intercurrent events comes first, 3 first prior intercurrent event indicator variables are created. ICECOVIN indicates which of three prior intercurrent events comes first: permanent discontinuation of IMP not due to the COVID-19 pandemic, rescue treatment not due to the COVID-19 pandemic, or subject-onset of the COVID-19 pandemic. ICECOVIN is used in the COVID-19 modified composite and hypothetical estimands. ICECOMIN indicates which of either rescue treatment or permanent discontinuation of IMP comes first including events due to the COVID-19 pandemic. ICECOMIN is used in the composite estimand. ICETREIN indicates which of either permanent discontinuation of IMP not due to the COVID-19 pandemic or

subject-onset of the COVID-19 pandemic comes first. ICETREIN is used in the treatment policy estimands.

Missing values due to the COVID-19 pandemic will be handled using the flag MISSCVFL which will only be assigned onto visits with no observed data.

As a convenience, estimand flags have been created for each estimand in order to select the correct data rows based on the intercurrent event indicator variables and the DTYPE variable. How data rows are selected for the primary analysis of each estimand can be seen in Table 9.

Table 9: Technical handling of intercurrent events and missing data in the primary analysis of the estimands

		Binary endpoints				Continuous endpoints		
Estimand flag		**EBICOVFL**	**EBICOMFL**	**EBITREFL**	**EBIHYFL**	**ECOHYFL**	**ECOTREFL**	**ECOCOVFL**
First prior intercurrent event indicator variable		**ICECOVIN**	**ICECOMIN**	**ICETREIN**	**ICECOVIN**	**ICECOVIN**	**ICETREIN**	**ICECOVIN**
First prior intercurrent event (indicator)	**Missing or observed data**	**COVID-19 modified composite**	**Composite**	**treatment policy**	**hypothetical**	**hypothetical[2]**	**treatment policy**	**COVID-19 modified composite**
Rescue treatment (RESCNCFL or RESCUEFL)[1]	**Missing data**	DTYPE=NRI	DTYPE=NRI	NA	DTYPE= MISSING	DTYPE= MISSING	NA	DTYPE= WOCF
	Observed data	DTYPE=NRI	DTYPE=NRI	NA	DTYPE= MISSING	DTYPE= MISSING	NA	DTYPE= WOCF
Permanent discontinuation of IMP (DISCNCFL or DISCONFL)[1]	**Missing data**	DTYPE=NRI	DTYPE=NRI	DTYPE= MISSING	DTYPE= MISSING	DTYPE= MISSING	DTYPE= MISSING	DTYPE= WOCF
	Observed data	DTYPE=NRI	DTYPE=NRI	DTYPE=''	DTYPE= MISSING	DTYPE= MISSING	DTYPE=''	DTYPE= WOCF
Subject-onset of the COVID-19 pandemic (SOC19FL)	**Missing data**	DTYPE= MISSING	NA	DTYPE= MISSING	DTYPE= MISSING	DTYPE= MISSING	DTYPE= MISSING	DTYPE= MISSING
	Observed data	DTYPE= MISSING	NA	DTYPE= MISSING	DTYPE= MISSING	DTYPE= MISSING	DTYPE= MISSING	DTYPE= MISSING
No prior intercurrent event ('')	**Missing data not due to the COVID-19 pandemic**	DTYPE=NRI	DTYPE=NRI	DTYPE= MISSING	DTYPE= MISSING	DTYPE= MISSING	DTYPE= MISSING	DTYPE= MISSING
	Missing data due to the COVID-19 pandemic	DTYPE= MISSING	DTYPE=NRI	DTYPE= MISSING	DTYPE= MISSING	DTYPE= MISSING	DTYPE= MISSING	DTYPE= MISSING
	Observed data	DTYPE=''	DTYPE=''	DTYPE=''	DTYPE=''	DTYPE=''	DTYPE=''	DTYPE=''

Abbreviations: NA = Not applicable; COVID-19 = Coronavirus Disease 2019; IMP = investigational medicinal product; RESCNCFL = rescue treatment not due to the COVID-19 pandemic flag; RESCUEFL = rescue treatment flag; DISCNCFL = permanent discontinuation of IMP not due to the COVID-19 pandemic; DISCONFL = permanent discontinuation of IMP; SOC19FL = subject-onset of the COVID-19 pandemic.

1) Which first prior intercurrent event indicator is used is dependent on the estimand.
2) If no post-baseline scheduled assessment exists, the last observation is carried forward (including baseline) with DTYPE='LOCF'.

6.8.6 Timing of intercurrent events

Actions taken based on intercurrent events will be dependent on whether or not an intercurrent event happens prior to a relevant visit. The rule will be that if any regarded intercurrent event happens prior to the date of the visit then the intercurrent event will be defined to be prior to the relevant visit. The following list of dates will be used in a prioritised manner as the date of the visit, i.e. if a date higher in the hierarchy exists that date will be used:

1. Observed date of the visit. When no data is available from the scheduled visit, data and visit date can be mapped to the visit per the rules stated in Section 6.8.4.

2. Planned date of the visit – 7 days, to account for the visit window.

In case intercurrent events occurs on the same date the following prioritise list will be used: rescue treatment, permanent discontinuation of IMP, and then subject-onset of the COVID-19 pandemic.

6.8.7 Rules for single imputation methods

Worst observation carried forward (WOCF) will be defined using the worst observation ever recorded between the baseline visit and the analysed visit (baseline assessment included). The date of the analysed visit will be defined as the observed date of the visit if existing, if not then the date of the planned visit + 7 days, i.e. the last assessment before or within the window for mapping an early termination visit or unscheduled visit to a planned visit.

The LOCF value will be used in some cases but only when data is missing and is defined as the last assessment obtained before the observed date of the visit if existing, if not then the planned date of the visit + 7 days.

6.8.8 Technical aspects of attributing events and missing data to the COVID-19 pandemic

Definition of identifying interference by the COVID-19 pandemic in comment fields/logs

In addendum 1, it was introduced that to attribute events to the COVID-19 pandemic the eCRF comments fields/log had to be used to identify when trial related procedures were interrupted due to the COVID-19 pandemic by writing “COVID-19”. However, alternative ways of specifying this should be accounted for and therefore if any comment fields/logs contain one of the following search terms it will be treated as equal to writing “COVID-19”:

"COVID" and "CORONA". Note, this will capture cases where there is written "CORONAVIRUS", as this would be included by the "CORONA" search term. All comments will be used in an uppercase format.

Permanent discontinuation of IMP due to the COVID-19 pandemic

Permanent discontinuation of IMP will be attributed to the COVID-19 pandemic if reason for permanent discontinuation of IMP contains a COVID-19 reference.

Missed visits due to the COVID-19 pandemic

Missed visits will be attributed to the COVID-19 pandemic if the eCRF comments log for the missed visit contains a COVID-19 reference.

Missed IMP doses due to the COVID-19 pandemic

Missed IMP doses can be attributed to the COVID-19 pandemic if one of the following occurs:

1. Missed visit due to the COVID-19 pandemic, implying that IMP dosing at that scheduled visit then also is missed due to the COVID-19 pandemic.

2. The eCRF comments field for the administration of IMP contains a COVID-19 reference.

Use of rescue treatment due to unavailability of IMP related to the COVID-19 pandemic

As stated in the protocol, attributing rescue treatment to the COVID-19 pandemic depends on either missed IMP dosing, missed visits or permanent discontinuation of IMP, due to the COVID-19 pandemic and thus the definition depends on the previous defined events.

Prolonged interruption of IMP due to the COVID-19 pandemic

As defined in the protocol and using the defined methods for missed IMP doses due to the COVID-19 pandemic and missed visits due to the COVID-19 pandemic.

Missing assessment data due to the COVID-19 pandemic

Assessment data missing will be attributed to the COVID-19 pandemic if one of the following occurs:

1. The visit where the assessment is scheduled to occur is missed due to the COVID-19 pandemic.

2. The visit where the assessment was scheduled to occur is not missing but is indicated to have been a telephone/video visit by having a COVID-19 reference in eCRF comment log implying that the assessment was not possible to do.

3. The eCRF comments field for the missing assessment data contains a COVID-19 reference.

6.8.9 Treatment labels

Table 10**: 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 Q2W + TCS	Tralokinumab Q2W + TCS	1
Treatment period	Placebo + TCS	Placebo + TCS	2

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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Reason for signing: Approved	Management / Lead Approver Verdict(s) Name: PPD Capacity: Biostatistics Date of signature: 21-Oct-2020 14:27:38 GMT+0000

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