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**Statistical Analysis Plan**

Study Code D2210C00014

Edition Number 2.0

Date 28 July 2017

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**A Multicentre, Randomized, Double-blind, Parallel Group, Placebo Controlled, 12-Week, Phase 2 Study to Evaluate the Effect of Tralokinumab on Airway Inflammation in Adults with Asthma Inadequately Controlled on Inhaled Corticosteroid (MESOS)**

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Study Statistician



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A & R Statistician



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**Global Product Statistician**



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## LIST OF ABBREVIATIONS

<b>Abbreviation or special term</b>	<b>Explanation</b>
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-Drug Antibodies
AE	Adverse Event
AHR	Airway Hyper-Responsiveness
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
ATC	Anatomical Therapeutic Chemical
ANCOVA	Analysis of Covariance
BD	Bronchodilator
BMI	Body Mass Index
CC	Clara-Cell
CI	Confidence Interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
C <sub>trough</sub>	Serum trough concentration
CV	Coefficient of Variation
DAE	AEs causing discontinuation of IP
DRMI	Dropout Reason-based Multiple Imputation
ECG	Electrocardiogram
DPP4	Dipeptidyl Peptidase-4
eCRF	Electronic Case Report Form
ECP	Eosinophil Cationic Protein
ER	Emergency Room
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome device
FAS	Full Analysis Set



<b>Abbreviation or special term</b>	<b>Explanation</b>
FEF <sub>25-75%</sub>	Forced Expiratory Flow at 25-75% of the forced vital capacity
FE <sub>NO</sub>	Fractional Exhaled Nitric Oxide
FEV <sub>1</sub>	Forced Expiratory Volume in 1 second
FRC	Functional Residual Capacity
FRI	Functional Respiratory Imaging
FVC	Forced Vital Capacity
GGT	S-Gamma-Glutamyl Transpeptidase
HU	Hounsfield Unit
IC	Inspiratory Capacity
ICS	Inhaled Corticosteroids
IgE	Immunoglobulin E
IL	Interleukin
IO	Impulse Oscillometry
IP	Investigational Product
IQR	Interquartile Range
ITT	Intent-to-Treat
LA	Lumen Area
LLOQ	Lower Limit of Quantification
MAR	Missing at Random
MBP	Major Basic Protein
MBW	Multiple Breath Washout
MCP	Monocyte chemoattractant protein
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
MUC5A	Mucin 5A
nAB	Neutralizing Antibodies
NC	Not calculable
NQ	Not Quantifiable
OAE	Other Significant Adverse Event
PEF	Peak Expiratory Flow

<b>Abbreviation or special term</b>	<b>Explanation</b>
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcome
PT	Preferred term
Q1	First Quartile
Q3	Third Quartile
RBM	Reticular Basement Membrane
RNA	Ribonucleic Acid
RV	Residual Volume
SAE	Serious Adverse Event
SABA	Short-Acting $\beta$ 2-Agonists
S <sub>acin</sub>	Index of acinar ventilation heterogeneity
SC	Subcutaneously
SD	Standard Deviation
SMA	Smooth Muscle Actin
SNOT-20	Sino-Nasal Outcome Test -20
SOC	System Organ Class
STAT 6	Signal Transducer and Activator of Transcription 6
TARC	Thymus and activation-regulated chemokine
TBL	Total Bilirubin
TGF	Transforming Growth Factor
TLC	Total Lung Capacity
UC	Urgent Care
ULN	Upper Limit of Normal
VC	Vital Capacity
WA	Wall Area

## AMENDMENT HISTORY

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Date	Brief description of change
25JUL2017	Updated to be consistent with STRATOS2; accounted for recent changes from protocol and changes on analyses; Removed duplicates in 4.2.5.2 Updated the five SNOT-20 categories to definition provided by study lead; no analyses on 5 domains. Updated SAP for consistency with Stratos 1 study. Updated strategy for ratio and percent changes analyses when baseline and or/ post-baseline records=0 Added sensitivity analyses for primary efficacy Clarified analysis for ADA/ PK Clarified record used for analyses for Sacin parameter

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## 1. STUDY DETAILS

This is the statistical analysis plan (SAP) for study D2210C00014. The SAP describes the statistical analyses specified in the clinical study protocol (CSP) in more detail; any changes with regards to what is already specified in the CSP will be described in Section 6.

### 1.1 Study objectives

#### 1.1.1 Primary objectives

Objective:	Outcome Measures:
To evaluate the effect of tralokinumab on eosinophilic airway infiltration in adult subjects with asthma inadequately controlled with inhaled corticosteroids (ICS).	<p><b>Primary outcome variable:</b> The change, expressed as a ratio, in number of airway submucosal eosinophils per mm<sup>2</sup> determined by microscopic evaluation of bronchoscopic biopsies from baseline up to Week 12.</p> <p><b>Primary outcome measure:</b> Ratio of tralokinumab to placebo at Week 12 to baseline.</p>

#### 1.1.2 Secondary Objectives

Secondary Objectives:	Outcome Measures:
To evaluate the effect of tralokinumab on blood eosinophil levels in adult subjects with asthma inadequately controlled with ICS.	<p><b>Outcome variable:</b> The change, expressed as a ratio, in number of blood eosinophils from baseline up to Week 12.</p> <p><b>Outcome measure:</b> Ratio of tralokinumab to placebo at Week 12 to baseline.</p>
To evaluate the effect of tralokinumab on sputum eosinophil levels in adult subjects with asthma inadequately controlled with ICS.	<p><b>Outcome variable:</b> The change, expressed as a ratio, in differential sputum eosinophils from baseline up to Week 12.</p> <p><b>Outcome measure:</b> Ratio of tralokinumab to placebo at Week 12.</p>

<b>Secondary Objectives:</b>	<b>Outcome Measures:</b>
To evaluate the effect of tralokinumab on activation of eosinophils in adult subjects with asthma inadequately controlled with ICS.	<p><b>Outcome variable:</b>            The change, expressed as a ratio, in number of blood and sputum free eosinophil cationic protein (ECP) from baseline up to Week 12.</p> <p><b>Outcome measure:</b>            Ratio of tralokinumab to placebo at Week 12 to baseline</p>

### 1.1.3 Safety objectives

<b>Safety Objective:</b>	<b>Outcome Measures:</b>
To evaluate the safety and tolerability of tralokinumab in adult subjects with asthma inadequately controlled with ICS.	<ul style="list-style-type: none"> <li>• Adverse Events (AE) /Serious Adverse Events (SAE)</li> <li>• Vital signs</li> <li>• Electrocardiograms (ECG)</li> <li>• Clinical chemistry/haematology/urinalysis</li> <li>• Physical examinations</li> </ul>

### 1.1.4 Exploratory objectives

<b>Exploratory Objectives:</b>	<b>Outcome Measures:</b>
<p>To evaluate the effect of tralokinumab on other biomarkers of airway inflammation in adult subjects with asthma inadequately controlled with ICS.</p>	<p>The change, from baseline up to Week 12 in number of eosinophils per mm<sup>2</sup> of epithelium and airway smooth muscle bundle determined by light microscopy of bronchoscopic biopsies from baseline up to Week 12.</p> <p>The change, from baseline up to Week 12 in number of inflammatory cells per mm<sup>2</sup> of epithelium, submucosa and airway smooth muscle bundle determined by light microscopy of bronchoscopic biopsies from baseline up to Week 12</p> <ul style="list-style-type: none"> <li>– CD3+, CD4+ and CD8+ lymphocytes,</li> <li>– Neutrophils,</li> <li>– Macrophages,</li> <li>– Mast cells</li> </ul>

Exploratory Objectives:	Outcome Measures:
	<p>Change from baseline up to Week 12 in induced sputum biomarkers:</p> <ul style="list-style-type: none"> <li>– Number of inflammatory cells (neutrophils, lymphocytes, macrophages) and epithelial cells per mL</li> <li>– Number of inflammatory cells (neutrophils, lymphocytes, macrophages) expressed as a percentage of total inflammatory cells</li> <li>– Biomarkers which may include (but are not limited to) histamine, leukotrienes, Interleukin (IL) IL-13, IL-5, IL-12, IL-31.</li> </ul> <p>Change from baseline up to Week 12 in serum biomarkers:</p> <ul style="list-style-type: none"> <li>– Which may include (but are not limited to) periostin, dipeptidyl peptidase-4 (DPP4), eotaxin, MCP1, TARC, IL-5, IL-33, STAT6, IL-13R<math>\alpha</math>2, MCP4/CCL13, TARC/CCL17, CLCA1, SERPINB2, biomarkers of tissue destruction, vascular-adhesion molecules</li> </ul> <p>Change from baseline up to Week 12 in biomarkers obtained from nasosorption samples (Optional)</p> <p>Change from baseline up to Week 12 in blood total Immunoglobulin E (IgE)</p> <p>Change from baseline up to Week 12 in fractional exhaled nitric oxide (FE<sub>NO</sub>)</p>

<b>Exploratory Objectives:</b>	<b>Outcome Measures:</b>
<p>To evaluate the effect of tralokinumab on large airways remodelling in adult subjects with asthma inadequately controlled with ICS</p>	<p>Change from baseline up to Week 12 in bronchial biopsy specimens:</p> <ul style="list-style-type: none"> <li>– Airway epithelial cell integrity (measured by light microscopy),</li> <li>– Lamina reticularis and reticular basement membrane (RBM) thickening (measured by light microscopy),</li> <li>– Deposition of periostin in basement membrane,</li> <li>– Mucus glands and mucin 5A (MUC5A),</li> <li>– Other biomarkers of tissue remodelling and/or destruction which may include (but are not limited to) <math>\alpha</math>-smooth muscle actin (SMA) and collagen type IV, fibronectin, laminin tenascin and transforming growth factor (TGF) <math>\beta</math> and epithelial damage markers which may include caspase 3 and clara-cell(CC)16/KL6,</li> <li>– Airway epithelial gene expression</li> </ul>
	<p>Change from baseline up to Week 12 in large airway dimensions and estimated airway resistance determined from computed tomography (CT)</p> <ul style="list-style-type: none"> <li>– Morphometry parameters (lumen area [LA], wall area [WA] and wall area %) for airway generations 3, 4 and 5 (segmental, sub-segmental, sub-sub-segmental),</li> <li>– Airway resistance for airway generations 3, 4 and 5 estimated based on lumen area,</li> <li>– Airway volume and resistance for entire airway tree (lobar or lung level) based on Functional Respiratory Imaging (FRI) (Optional)</li> </ul>



<b>Exploratory Objectives:</b>	<b>Outcome Measures:</b>
<p>To evaluate the effect of tralokinumab on small airways remodelling in adult subjects with asthma inadequately controlled with ICS</p>	<p>Change from baseline up to Week 12 in</p> <ul style="list-style-type: none"> <li>– R5-R20 and AX as evaluated by Impulse Oscillometry (IO),</li> <li>– <math>S_{acin}</math> (Index of acinar ventilation heterogeneity) by using multiple breath washout (MBW),</li> <li>– Air trapping expressed as percentage of the lung with expiratory density less than -856 HU, and as expiratory-to-inspiratory ratio of mean lung density on CT,</li> <li>– Regional matching of the inspiratory/expiratory CT scans to assess air trapping/small airway obstruction,</li> <li>– Extent of gas trapping determined from physiologic testing by total lung capacity (TLC)/ residual volume (RV)/ vital capacity (VC)/inspiratory capacity (IC)/functional residual capacity (FRC)</li> </ul>
<p>To evaluate the effect of tralokinumab on asthma symptoms and other asthma control metrics in adult subjects with asthma inadequately controlled with ICS</p>	<p>Change from baseline up to Week 12 in</p> <ul style="list-style-type: none"> <li>– Daily asthma symptom scores (combined daytime and night-time score)</li> <li>– Rescue medication use</li> <li>– Home peak expiratory flow (PEF) (morning and evening)</li> <li>– Number of night-time awakening due to asthma</li> <li>– Asthma Control Questionnaire 6 (ACQ-6)</li> </ul>

<b>Exploratory Objectives:</b>	<b>Outcome Measures:</b>
To evaluate the effect of tralokinumab on lung function and bronchial hyper-responsiveness in adult subjects with asthma inadequately controlled with ICS	Change from baseline up to Week 12 in pre BD (Bronchodilator) and post BD spirometry <ul style="list-style-type: none"> <li>– Forced expiratory volume in 1 second (FEV<sub>1</sub>),</li> <li>– Forced vital capacity (FVC),</li> <li>– Forced expiratory flow between 25% and 75% of the forced vital capacity (FEF<sub>25-75%</sub>),</li> </ul> Change from baseline up to Week 12 in <ul style="list-style-type: none"> <li>– Airway Hyper-responsiveness (AHR).</li> </ul>
To evaluate the effect of tralokinumab on symptom metrics of rhinosinusitis in adult subjects with asthma inadequately controlled with ICS	Change from baseline up to Week 12 in Sino-Nasal Outcome Test -20 (SNOT-20) total score
To evaluate the pharmacokinetics and immunogenicity of tralokinumab	Pharmacokinetic parameters: C <sub>trough</sub> (Serum trough concentration)  Immunogenicity outcome variables: incidence rate of positive anti-drug antibodies (ADA) and characterization of their neutralizing potential
To evaluate the effect of tralokinumab on Ribonucleic Acid (RNA) in samples obtained from adults subjects with asthma inadequately controlled with ICS	

Results from some exploratory analyses, if performed, may be reported separately from the Clinical Study Report (CSR).

## 1.2 Study design

This multicentre, randomized, double-blind, parallel group, placebo-controlled, phase 2 study will evaluate the effect of a 300 mg dose of tralokinumab administered subcutaneously (SC) every 2 weeks on airway inflammation in adults with asthma inadequately controlled on ICS ( $\geq 250$  mcg fluticasone dry powder formulation equivalents total daily dose) with or without other controllers.

The subjects (males and females, 18 to 75 years of age at screening inclusive) will be randomized to 12-Week treatment with tralokinumab or placebo (1:1).

Approximately 80 subjects will be randomized.

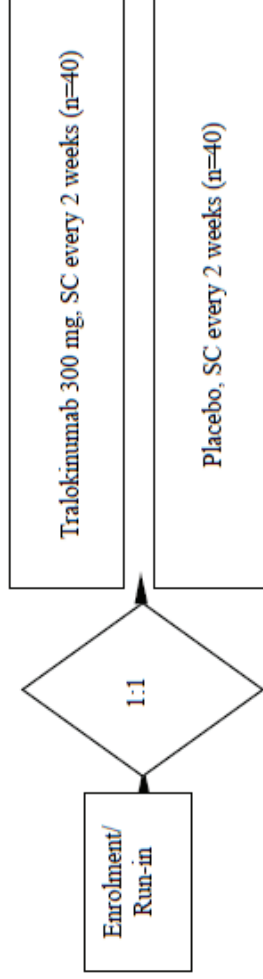
After initial enrolment and confirmation of entry criteria, subjects will proceed to a run-in period of 4 weeks during which their suitability for randomisation will be confirmed. Subjects who meet the eligibility criteria at visit 3c will be randomized to a 12-week treatment period. The subjects' currently prescribed ICS and additional asthma controller medication will remain unchanged during the run-in and treatment period.

EOT (End of Treatment) visit will be at Week 12 (Visit 9). Post-treatment follow-up period for all subjects will be for 14 Weeks after the EOT visit with a telephonic follow-up (FU) 1 visit (Visit 10, Week 16). There will be an on-site FU 2 visit (Visit 11, Week 26) for WOCBP only, to also ascertain their pregnancy status. For all other subjects this will be a telephonic FU 2 visit.

A graphical view of the study is shown in [Figure 1](#).

**Figure 1** Study flow chart

Visit 1, 2, 3a, 3b	Visit 3c <sup>1</sup>	Visit 4 to 8	Visit 9	Visit 10, 11 <sup>2</sup>
Enrolment/ Run-in Week -4, -2, -1	Randomization Week 0	12-week double-blind randomized Treatment period Week 0 up to Week 10	End of Treatment Week 12	Follow-up Week 16, 26 <sup>2</sup>



1. Due to multiplicity of assessments, Visit 3 is spread over 3 visits, Visit 3a, 3b and 3c. Visit 3c being the randomization visit when IP is administered for the first time.
2. WOBCP will have an on-site follow-up visit at Week 26 to also ascertain their pregnancy status.

### 1.3 Number of subjects

The study is powered to show a reduction in airway submucosal eosinophils, from baseline to Week 12 (Visit 9) for tralokinumab, versus placebo in the overall study population.

The sample size is based on the primary endpoint; change from baseline to Week 12 (Visit 9) in airway submucosal eosinophils. Given an assumed deviation of the log values in the 2 treatment groups are 1.62 and 1.82 it is estimated that 31 subjects in each treatment arm will be sufficient to achieve at least 80% power to detect a 3.5-fold difference versus placebo using a two-sided test at 5% significance level. It is assumed that a non-neglectable proportion of the subjects will not have an evaluable primary endpoint value due to failed biopsies. To account for this, 40 subjects will be randomized in each treatment arm.

## 2. ANALYSIS SETS

### 2.1 Definition of analysis sets

**All subjects analysis set:** This analysis set comprises all subjects screened for the study and will be used for the reporting of disposition and screening failures.

#### 2.1.1 Efficacy analysis set

**Full analysis set (FAS):** All subjects randomized and receiving any investigational product (IP) will be included in the FAS, irrespective of their protocol adherence and continued participation in the study. Subjects will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued. For subjects who withdraw consent or assent to participate in the study all data will be included up to the date of their study termination.

#### 2.1.2 Safety analysis set

**Safety analysis set (Safety):** All subjects who received any IP will be included in the safety analysis set. Subjects will be classified according to the treatment they actually received. A subject who has, on one or several occasions, received active treatment will be classified as active. A subject who has received only Placebo will be classified as Placebo. All safety and ADA summaries will be based on this analysis set.

Any deviation from the randomized treatment assignment will be listed and considered when interpreting the safety data.

#### 2.1.3 Pharmacokinetic analysis set

**Pharmacokinetic (PK) analysis set:** All subjects in the full analysis set who received tralokinumab and who had blood samples obtained for PK, including PK blood samples that are assumed not to be affected by factors such as protocol deviations (eg, - disallowed medication, or incorrect study medication received) will be included in the analysis set. All PK summaries will be based on this analysis set.

#### **2.1.4 Patient reported outcome (PRO) analysis set**

PRO outcome variables will be evaluated based on the FAS.

All efficacy analyses will be performed using an Intent-to-Treat (ITT) approach based on the FAS. For consistency, demographic and baseline characteristics will be presented using the FAS. Safety objectives will be analyzed based on the Safety analysis set.

## **2.2 Violations and deviations**

Only important protocol deviations will be listed and tabulated in the CSR for all randomized subjects. These are protocol deviations that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being include:

- Subjects who do not meet the inclusion criteria
- Subjects who do not meet the randomization criteria
- Subjects who meet any of the exclusion criteria
- Subjects who use one or more disallowed medication, or restricted medications outside of the restrictions defined in the CSP, (for any reason, unless otherwise specified) during the randomized treatment period
- Subjects who received the incorrect IP or study dose at any time during the 12-Week double-blind treatment period
- Subjects who developed withdrawal criteria during the study but were not withdrawn from IP

All important protocol deviations will be identified and documented by the AZ study physician and statisticians prior to unblinding of the data.

## **3. PRIMARY AND SECONDARY VARIABLES**

### **3.1 General Definitions**

#### **3.1.1 Definition of baseline**

For outcome variables based on efficacy biomarkers and pre-bronchodilator (BD) and post-BD spirometry (FEV<sub>1</sub>, FVC and FEF<sub>25-75%</sub>) and AHR the measurement recorded at Visit 3 (a, b or c) will be used as baseline. If the Visit 3 measurement is missing or the measurement is not scheduled to be measured at Visit 3, the last non-missing value before Visit 3 will be used as baseline instead. For reversibility (see Section 3.1.3), the baseline will be the first measurement when the reversibility assessment was considered complete .

The baseline for Electronic Patient Reported Outcome (ePRO) variables will be captured or derived from what is captured on the ePRO device at Visit 3c. Derivations are described in the relevant parts of Section 3.3.

Baseline for Asthma Daily Diary variables will be the bi-weekly mean for data collected between the evening of day -14 and the morning of day 1, where day 1 is the day of randomization. If more than 7 daily measures/scores (>50%) within a period is missing, then the bi-weekly mean for that period will be set to missing.

For laboratory data, vital signs and physical examination, baseline will be defined as the latest non-missing assessment prior to first dose. If no time is recorded for an assessment, and the assessment takes place at Visit 3, this will be assumed to be a pre-dose assessment. For ECG the measurement recorded at Visit 1 will be used as baseline.

### 3.1.2 Absolute and percent change from baseline

Absolute change from baseline outcome variables is computed as

$$(post-randomization\ value - baseline\ value).$$

Percent change from baseline is computed as

$$((post-randomization\ value - baseline\ value) / baseline\ value) \times 100\%.$$

Ratio of post-randomization value to baseline value is computed as

$$(post-randomization\ value / baseline\ value).$$

For the analysis of ratios, a log transformation is required. If either the post-randomization value or the baseline value is missing, then the absolute or percent change from baseline or the ratio value will also be set to missing.

### 3.1.3 Reversibility

Reversibility percentage will be computed at baseline as

$$\% \text{ Reversibility} = (post-BD\ FEV_1 - pre-BD\ FEV_1) \times 100 / pre-BD\ FEV_1$$

The FEV<sub>1</sub> post-BD measurement in the reversibility derivation will be the latest measurement and can be the post-BD measurement after 4, 6 or 8 SABA (short-acting β<sub>2</sub>-agonists) inhalations, depending on when the reversibility assessment was considered complete.

### 3.1.4 Visit and period windows

For local laboratory data, vital signs, physical examination, and ADA, the visit recorded in the Web Based Data Capture system will be used.

For the efficacy assessments, central laboratory results, spirometry, ACQ-6 and SNOT-20, the variables will be summarized based on the scheduled days with adjusted analysis-defined visit windows as defined in [Table 1](#).

Any data collected at unscheduled visits will be listed, included within baseline data in shift plots, and will be included in the definition of maximum/ minimum within-period value, but will not be included in summaries by visit. In case of a missing assessment at a scheduled visit followed by an unscheduled visit, the unscheduled assessment will not replace the missing result in the summary outputs by period and visit.

If appropriate, i.e. if a substantial percentage of observations for a secondary efficacy variable falls outside the adjusted window, a sensitivity analysis will be performed where observations are assigned according to the extended windows in [Table 1](#).

**Table 1** Visit windows

Visit	Target Day	Adjusted windows for analyses:	Extended windows for sensitivity analyses:
			Blood eosinophils count; Differential sputum eosinophils; Blood eosinophils and sputum free ECP
Baseline (Week 0) <sup>a</sup>	1	1	1
Week 2	15	2-21	-
Week 4	29	22-35	-
Week 6	43	36-49	2-63
Week 8	57	50-63	-
Week 10	71	64-77	-
Week 12	85	78-99	64-99
Week 16 (FU1)	113	100-147	-
Week 26 (FU2)	183	148-217	

<sup>a</sup> If the Day 1 assessment is missing, see section 3.1.1 on how baseline value is defined.

For assignment of data to time points using the visit windows, study day will be defined as follows for efficacy data:

$$(\text{Date of assessment} - \text{Date of randomisation}) + 1.$$

And as follows for safety endpoints:

$$(\text{Date of assessment} - \text{Date of first dose of IP}) + 1.$$



In case of multiple observations within a single visit window, the following rules apply:

- If there are two or more observations within the same visit window, the non-missing observation closest to the target day will be used in the analysis
- If two observations are the same distance from the target day, the non-missing observation with the earlier collection date will be used in the analysis
- If two observations are collected on the same day and have a collection time associated with them, the non-missing observation with the earlier collection time will be used in the analysis
- If two or more observations are collected on the same day, all non-missing but with no collection time associated with at least one of them, the average of the observations will be used in the analysis.

If a visit window does not contain any observation, then the data will be missing for that visit.

## **3.2 Calculation or derivation of efficacy variables**

### **3.2.1 Primary Variable**

#### **3.2.1.1 Number of airway submucosal eosinophils per mm<sup>2</sup>**

The primary endpoint is the change, expressed as a ratio, in the number of airway submucosal eosinophils per mm<sup>2</sup> determined by microscopic evaluation of bronchoscopic biopsies from baseline to Week 12 (Visit 9). The ratio of Week 12 (Visit 9) to baseline will be calculated as described in Section 3.1.2.

Absolute change from baseline to Week 12 (Visit 9) will also be calculated and is considered as a supportive variable to the primary variable.

### **3.2.2 Secondary Variables**

#### **3.2.2.1 Blood eosinophil count**

The change, expressed as a ratio, in the blood eosinophil count from baseline to Week 12 (Visit 9) is a secondary endpoint. The ratio of Week 12 (Visit 9) to baseline will be calculated as described in Section 3.1.2.

Absolute change from baseline to Week 12 (Visit 9) will also be calculated and is considered as a supportive variable.

#### **3.2.2.2 Differential sputum eosinophils**

The change, expressed as a ratio, in differential sputum eosinophils (as a marker for activated eosinophils) from baseline to Week 12 (Visit 9) is a secondary endpoint. The ratio of Week 12 (Visit 9) to baseline will be calculated as described in Section 3.1.2.

Absolute change from baseline to Week 12 (Visit 9) will also be calculated and is considered as a supportive variable.

### **3.2.2.3 Blood eosinophils and sputum free eosinophils cationic protein**

The change, expressed as a ratio, in blood and sputum free ECP concentrations from baseline up to Week 12 (Visit 9) is a secondary endpoint. The ratio of Week 12 (Visit 9) to baseline will be calculated as described in Section 3.1.2 and compared between treatments. Absolute change from baseline to Week 12 (Visit 9) will be calculated as a supportive variable.

## **3.2.3 Efficacy Exploratory Variables**

### **3.2.3.1 Biomarkers for airway inflammation**

The change from baseline to Week 12 (Visit 9) will be calculated as described in Section 3.1.2, and separately expressed as absolute change, percent change, for all exploratory endpoints:

- The number of eosinophils per mm<sup>2</sup> of epithelium and airway smooth muscle bundle.
- Inflammatory cell counts/mm<sup>2</sup> of epithelium, submucosa and airway smooth muscle bundle for:
  - CD3+, CD4+, CD8+ lymphocytes
  - Neutrophils
  - Macrophages
  - Mast Cells.
- Induced sputum for:
  - Number and percentage of neutrophils, lymphocytes and macrophage as percentage number of inflammatory cells
- Serum:
  - Biomarkers which may include (but are not limited to) periostin, DPP4.
- Blood total IgE.
- FE<sub>NO</sub>.

### 3.2.3.2 Effect on large airways remodelling

The change from baseline to Week 12 (Visit 9) will be calculated as described in Section 3.1.2 for the following exploratory endpoints:

- Airway epithelial cell integrity.
- Lamina reticularis and RBM thickening.
- Deposition of periostin in basement membrane.
- Mucus glands and MUC5A.
- Biomarkers of tissue remodelling and/or destruction which may include but are not limited to  $\alpha$ -SMA and collagen type IV, fibronectin, laminin tenascin and TGF $\beta$  and epithelial damage markers which may include caspase 3 and CC16/KL6
- Large airway dimensions and estimated airway resistance determined from CT:
  - Morphology parameters (Lumen area, wall area and wall area %) for airway generations 3, 4 and 5 (segmental, sub-segmental). For these analyses, only the percent change will be considered. In case of several records per subject/ parameter/ visit, the subject/ parameter/ visit average will be calculated first. The percent change from baseline will then be calculated for each subject/ parameter. Analyses will then be done separately for RB1 and LB1+2. The average percent change from baseline will also be calculated across all segmental parameters, and across all sub-segmental parameters; then summarized separately.
  - Airway resistance for airway generations 3, 4 and 5 estimated based on lumen area (airway resistance=(Lumen Area)<sup>-2</sup>). For these analyses, only the percent change will be considered. In case of several records per subject/ parameter/ visit, the subject/ parameter/ visit average will be calculated first. The percent change from baseline will then be calculated for each subject/ parameter. Analyses will then be done separately for RB1 and LB1+2. The average percent change from baseline will also be calculated across all segmental parameters, and across all sub-segmental parameters; then summarized separately.

### 3.2.3.3 Effect on small airway obstruction

The change from baseline to Week 12 (Visit 9) will be calculated as described in Section 3.1.2 for the following exploratory endpoints:

- R5-R20 and AX as evaluated by AO
- S<sub>acin</sub> by using MBW

- Air trapping expressed as percentage of the lung with expiratory density less than -856 HU, and as expiratory-to-inspiratory ratio of mean lung density on CT
- Regional matching of the inspiratory/expiratory CT scans to assess air trapping/small airway obstruction
- Extent of gas trapping determined from physiologic testing by TLC/RV, VC/IC, FRC

For the Sacin parameter, the value used for the analyses will be the average of the records of day of all quality values (1 or 2) – quality=3 records will not be considered for the analyses. Once the daily value is obtained, the usual baseline/visit window defined in this SAP will apply.

#### **3.2.3.4 Lung function and bronchial hyper-responsiveness**

The change from baseline to Week 12 (Visit 9) will be calculated as described in Section 3.1.2 for the following exploratory endpoints:

- FEV<sub>1</sub> (Pre-BD and Post-BD)
- FVC (Pre-BD and Post-BD)
- FEF<sub>25-75%</sub> (Pre-BD and Post-BD)
- AHR PD20, AHR PC20

FEV<sub>1</sub>, FVC and FEF<sub>25-75%</sub> will be determined by spirometry. To ensure quality control all spirometries are reviewed to ensure that they meet ATS/ERS criteria for acceptability. Only those spirometry tracings determined to be acceptable or borderline will be used to determine FEV<sub>1</sub>, FVC and FEF<sub>25-75%</sub>, based on the best measurement selected by ERT per spirogram. Section 5.1.8 of the CSP contains further details of the spirometry recordings.

The percentage change from baseline to Week 12 (Visit 9) described in Section 3.1.2 will also be calculated for AHR PD20/ AHR PC20 as a supportive variable.

#### **3.2.3.5 Asthma Exacerbations**

For the purpose of the study, an asthma exacerbation will be defined as a worsening of asthma that leads to any of the following:

- A temporary bolus/burst of systemic corticosteroids for at least 3 days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids
- An emergency room (ER) or urgent care (UC) visit due to asthma that required systemic corticosteroids (as per the above)

- An in-patient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for  $\geq 24$  hours) due to asthma

Worsening of asthma is defined as new or increased symptoms and/or signs (examination or lung function) that can be either concerning to the subject (subject-driven) or related to an asthma daily diary alert (diary-driven). Baseline values for Asthma Daily Diary variable will be the average of all the daily records within the Visit 1 and Visit 2.

The eDiary will be programmed to alert both the subject and study centre when certain prespecified worsening thresholds are crossed.

Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

In order to calculate the number of exacerbations experienced by a subject during the 12-week treatment period the following rule will be applied:

- The start of an exacerbation is defined as the start date of systemic corticosteroids, ER or UC visits requiring systemic steroids or hospital admissions due to asthma, whichever occurs earlier.
- The end date is defined as the last day of systemic corticosteroids or ER or UC visit or hospital discharge, whichever occurs later.

An asthma exacerbation that occurs  $\leq 7$  days since the last dose of systemic steroids, prescribed for a prior exacerbation, will be counted as the same exacerbation event.

For the production of summary statistics, the annual exacerbation rate per subject is calculated, and standardized according per a 52-week period according to the formula described below.

*Annual Exacerbation Rate = No. of Exacerbations \* 365.25 / (last Follow-up date – Date of randomization + 1).*

### **3.3 Calculation or derivation of patient reported outcome variables**

Patient-reported outcomes data will be captured via an ePRO device. The definition of exploratory outcome variables based on the ePRO are provided in the following sections.

For asthma symptom score, rescue medication use and home PEF, bi-weekly means will be calculated. A bi-weekly mean is calculated as the sum of all non-missing daily measures/scores over 14 sequential days before a visit, up to an including the morning recording on the day of that visit (if appropriate), divided by the number of non-missing daily measures/scores during the same 14 days. Where a total measure/score that encompasses the sum/combination of daytime and night-time diary entries is calculated, the night-time recording for a given day will be the entry recorded the same morning (e.g. if the first IP

administration happens on Day 1, the first total measure/score that can be calculated is for Day 2 and will be the combination of the night-time measure/score recorded on the morning of Day 2 plus the daytime measure/score recorded on the evening of Day 2).

For nights with awakenings due to asthma, the bi-weekly mean will be the percentage of times the subject answered “yes” to ‘did your asthma cause you to wake up’ and “yes” to ‘did you use rescue medication upon awakening’. If more than 7 daily measures/scores (>50%) within a period is missing, then the bi-weekly mean for that period is set to ‘missing’.

### **3.3.1 PRO Exploratory Variables**

#### **3.3.1.1 Asthma symptom score**

Asthma symptoms during daytime and night-time will be recorded by the subject each evening and morning in the ePRO tool. Symptoms will be recorded using a scale 0-3, where 0 indicates no asthma symptoms. Asthma symptom daytime score (recorded in the evening and referring to the current day), night-time score (recorded in the morning and referring to the night before), and total score will be calculated and presented separately.

The daily asthma symptom total score will be calculated by taking the sum of the daytime and the night-time asthma symptom scores within a day. If a subject is missing a value for either night-time or daytime asthma symptom score on a given day then the total score for that day will be set to missing.

The outcome variable is the bi-weekly mean daily asthma symptom total score. The Week 12 (Visit 9) bi-weekly mean will be the sum of the daily total scores for 14 sequential days up to and including the total score calculated for the day before the Week 12 (Visit 9) visit divided by the number of non-missing daily total scores during the same 14 days.

Bi-weekly means for daytime and night-time scores will also be calculated. The Week 12 (Visit 9) bi-weekly mean daytime score will be the sum of the daytime scores for 14 sequential days up to and including the daytime score entered on the evening before the Week 12 (Visit 9) visit divided by the number of non-missing daytime scores during the same 14 days.

The Week 12 (Visit 9) bi-weekly mean night-time score will be the sum of the night-time scores for 14 sequential days up to and including the night-time score entered on the morning of the Week 12 (Visit 9) visit divided by the number of non-missing night-time scores during the same 14 days.

The number of asthma symptom-free days will be calculated for each subject as the total number of days in the 12week treatment period where the total asthma symptom score is 0. The proportion of asthma symptom-free days will be calculated using the total number of days with completed asthma symptom score diary during the 12week treatment period as the denominator.

### 3.3.1.2 Rescue medication use

The number of rescue medication inhalations and nebulizer treatments taken will be recorded by the subject in the ePRO twice daily. Daytime use is recorded in the evening and night-time use is recorded in the morning. Inhaler usage will be reported as the number of puffs in a given period whereas nebulizer use will be reported as the number of times.

The number of inhalations of rescue medication and nebulizer treatments captured in the eDiary each day will be calculated per subject. If a subject is missing a value for either night-time or daytime rescue medication on a given day, then the total rescue medication use for that day will be set to missing.

The number of inhalations (puffs) per day will be calculated as follows:

*Number of night inhaler puffs + 2 x [number of night nebulizer times] + number of day inhaler puffs + 2 x [number of day nebulizer times].*

Bi-weekly mean number of inhalations (puffs) per day will be calculated as the outcome variable. The Week 12 (Visit 9) bi-weekly mean will be the number of inhalations (puffs) for 14 sequential days up to and including the number of inhalations (puffs) calculated for the day before the Week 12 (Visit 9) visit divided by the number of non-missing daily total scores during the same 14 days.

### 3.3.1.3 Nights with awakening due to asthma

Bi-weekly mean number (expressed as percentage) of nights with awakening due to asthma that required rescue medication will be calculated as the outcome variable. The bi-weekly mean number (percentage) calculation for Week 12 (Visit 9) will include the night-time entries on 14 sequential days up to and including the entries on the morning of the Week 12 (Visit 9) visit.

### 3.3.1.4 Home peak expiratory flow (morning and evening)

Bi-weekly mean changes from baseline in morning (night-time) and evening (daytime) PEF will be calculated as the outcome variable. The Week 12 (Visit 9) bi-weekly mean daytime and night-time PEF will be as described for daytime and night-time asthma symptom scores in Section 3.3.1.1.

### 3.3.1.5 Asthma Control Questionnaire (ACQ-6)

In the ACQ-6 questionnaire the subjects are asked to recall the status of their asthma during the previous week with regards to symptom and use of short acting  $\beta$ -agonists. The questionnaire include questions on

1. Awoken at night by symptoms
2. Limitation of normal daily activities
3. Waking in the morning with symptoms

4. Dyspnoea
5. Wheeze
6. Daily rescue medication

The questions of the ACQ-6 are measured on a 7-point scale scored from 0 (totally controlled) to 6 (severely uncontrolled). The ACQ-6 score is computed as the un-weighted mean of the responses to the 6 questions. If response to any of the questions is missing, the ACQ-6 score will be missing.

The outcome variable for the ACQ-6 will be the change in mean score from baseline to each of the post-randomization assessments. The change from baseline for each question will also be calculated.

Other variables based on ACQ-6 to report include:

- ACQ-6-responder (Yes=1/No=0)
  - Responder: Change from baseline ACQ-6 score  $\leq -0.5$
  - Non-responder: Change from baseline ACQ-6 score  $> -0.5$
- ACQ-6-response (Improved/No Change / Deterioration)
  - Improvement: Change from baseline ACQ-6 score  $\leq -0.5$
  - No change:  $-0.5 < \text{Change from baseline ACQ-6 score} < 0.5$
  - Deterioration: Change from baseline ACQ-6 score  $\geq 0.5$
- Subjects asthma control as measured by ACQ-6 score:
  - Well controlled : ACQ-6 score  $\leq 0.75$
  - Partly controlled:  $0.75 < \text{ACQ-6 score} < 1.5$
  - Not well controlled: ACQ-6 score  $\geq 1.5$

The ACQ-6-responder, the ACQ-6-response, and subject asthma control variables will be analysed only considering non-missing ACQ-6 values.

### 3.3.1.6 Sino-Nasal Outcome Test - 20 (SNOT-20)

In the SNOT-20 the subjects are asked to recall their experiences during the previous 2 weeks and to score each of the 20 questions [divided across five subgroups 1) nasal symptoms, 2) paranasal symptoms, 3) sleep-related symptoms, 4) individual impairment 5) social impairment and emotional impairment] on a 6-point scale ranging from 0 (no problem) to 5



(most serious problem). In addition they are asked to record which of the five subgroups they consider to be the most important. The total score is calculated as the sum of the responses to all questions answered. There will be no imputation for missing data.

The outcome variable for the SNOT-20 will be the change in total score from baseline to Week 12 (Visit 9).

For each question and visit, the number and percentage of subjects who ticked the corresponding question as “most important” will be summarised.

### **3.4 Calculation or derivation of safety variable(s)**

The following safety data will be collected: vital signs, physical examination, 12-lead ECG, haematology, clinical chemistry, urinalysis, and reported AEs.

Change from baseline to each post-baseline time point where scheduled assessments were made will be calculated for relevant measurements.

#### **3.4.1 Adverse events**

Adverse events experienced by the subjects will be collected throughout the entire study and will be coded by the AstraZeneca designee using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse event data will be categorized according to their onset date into the following study periods:

- AEs occurring during run-in (onset date  $\geq$  Visit 1 and before the first dose of IP)
- AEs occurring during treatment (onset date  $\geq$  the first day of IP and  $\leq$  the last day of IP + 2 weeks)
- AEs occurring post-treatment (onset date  $>$  the last day of IP + 2 weeks and  $\leq$  Visit 11 (Week 26))

The timing of AEs will be assigned to the period in which they first occurred. If an AE has a missing onset date, then unless the stop date of the AE indicates otherwise, this will be considered an on treatment event. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered an on treatment AE. The same ‘during treatment’ definition will be used for laboratory and physical examination data, where applicable.

#### **3.4.2 Safety topics of special attention**

Although the CSP did not describe AEs of special interest, AstraZeneca Patient Safety and study physicians will review all AEs and identify those that merit special attention. These AEs fall into three categories, AEs possibly related to administration of biologics (e.g., anaphylaxis/hypersensitivity reactions and injection site reactions), AEs possibly related to the mechanism of action of tralokinumab as an IL-13 blocking agent (e.g., infections such as

severe, viral, invasive fungal, and parasitic, malignancy, cardiovascular/cerebrovascular events, pregnancy/spontaneous abortion and increased eosinophils) and AEs reported for other biologics in this class (e.g., musculoskeletal). AEs falling into the category of safety topics of special attention will be tabulated.

### 3.4.3 Laboratory variables

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times detailed in the CSP. Blood samples for determination of haematology/haemostasis and clinical chemistry will be performed at a central laboratory. Urine samples will be analyzed locally and sent for analysis at the central lab only when a positive dipstick result for any parameter is observed. The parameters outlined in Table 2 in Section 5.2.1 of the CSP, will be collected. Laboratory data will be reported in SI units.

Changes in haematology and clinical chemistry variables between baseline and each subsequent scheduled assessment will be calculated.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). The AstraZeneca extended reference ranges will be used for laboratory variables (where they exist). All values (absolute and change) falling outside the reference ranges will be flagged.

Urinalysis data will be categorised as negative (0), trace, or positive (+) at each time-point.

For the purposes of haematology, clinical chemistry and urinalysis shift tables on-treatment will be defined as the latest non-missing assessment whilst the subject is ongoing on treatment, using the 'during treatment' definition as defined in Section 3.4.1.

For the liver function tests: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline phosphatase (ALP), S-Gamma-glutamyl transpeptidase (GGT) and total bilirubin (TBL), the multiple of the AstraZeneca upper limit of the normal (ULN) (not extended) range will be calculated for each data point.

$$\text{Multiple} = \text{Value} / \text{ULN}$$

i.e., if the ALT value was 72 IU/L (ULN 36) then the multiple would be 2.

Subjects who meet any of the following criteria at any point during the study will be flagged:

- $\text{AST} \geq 3x \text{ ULN}$
- $\text{ALT} \geq 3x \text{ ULN}$
- $\text{TBL} \geq 2x \text{ ULN}$

### 3.4.4 ECGs

Twelve-lead ECG measurements will be recorded in accordance with the protocol.

The outcome of the overall evaluation is to be recorded as normal/abnormal in the electronic case report form (eCRF), with any abnormalities being recorded as not clinically significant or clinically significant.

### **3.4.5 Physical examination**

Complete and brief physical examinations will be performed at time points specified in Table 1 in the CSP. What is included in the assessment will be dependent on whether the examination is complete or brief, as described in Section 5.1.7 of the CSP. For the brief physical examination, only information on whether the assessment was performed or not will be recorded.

Each component of the baseline visit complete physical examination will be recorded as normal or abnormal. Each component of the follow-up complete physical examinations will be recorded as normal, same as baseline, or new/aggravated.

On-treatment will be defined as the latest non-missing assessment whilst the subject is ongoing on treatment, using the ‘during treatment’ definition as defined in Section 3.4.1.

### **3.4.6 Any new finding(s), or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE. Vital signs**

Pre-dose vital signs (pulse, systolic blood pressure, diastolic blood pressure, respiration rate and body temperature) will be obtained in accordance with the schedule provided in Table 1 in the CSP.

Changes in vital signs variables between baseline and each subsequent scheduled assessment will be calculated.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

Body mass index (BMI) will be summarised from the height (in meters) and weight (in kilograms) as follows:

$$BMI = kg/m^2$$

### **3.4.7 Medical History**

The principal for imputing incomplete diagnosis dates when calculating the number of years since diagnosis (earliest possible date) is shown in the table below:

**Table 2 Approach to incomplete diagnosis dates for medical history**

<b>Date of Birth</b> (Year-Month-Day)	<b>Diagnosis Date</b> (Year-Month-Day)	<b>Date for use in calculations</b> (Year-Month-Day)
1951-09-16	1951-10-10	1951-10-10
1951-09-16	1951-10-UK	1951-10-01
1951-09-16	1951-UK-UK	1951-10-16
1951-09-16	1952-UK-UK	1952-01-01

UK=Unknown

### **3.5 Calculations or derivation of Pharmacokinetic and Immunogenicity variables**

Blood samples (processed to serum) for PK and immunogenicity assessments will be collected from all subjects at baseline prior to first IP administration at Week 0 (Visit 3) and at Week 12 (Visit 9) before IP administrations (except for visit 9, where there is no drug administration). ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer). These validated methods are conducted using a bridging assay format and statistically determined floating screening assay cut point factor and confirmatory assay cut point. The minimal sample dilution is 1:13. Titer values are reported as the reciprocal of the highest dilution that yields a value above the cut point. Samples from pre-defined study time points that confirm positive for ADA will also be tested for neutralizing ADA (nAb) activity. Both ADA and nAb will be summarized using descriptive statistics as described in Section 4.2.9.67.

#### **Pharmacokinetics and immunogenicity of tralokinumab:**

Tralokinumab serum concentrations will be tabulated by visit along with descriptive statistics. Population PK modelling may also be performed to better characterize the PK of tralokinumab, but will be reported separately from the CSR.

If possible and if relevant, the impact of ADA occurrence on the PK and PD and safety will be summarized in the CSR.

## **4. ANALYSIS METHODS**

### **4.1 General principles**

The analysis of the study endpoints will include all data captured during the 12-week double-blind treatment period. This includes data regardless of whether IP was prematurely discontinued or delayed, and/or irrespective of protocol adherence, unless the subject withdraws consent to study participation.

Only exacerbations confirmed to meet the protocol definition (CSP Section 5.1.12) will be included in exploratory summaries. This includes only exacerbations that started on or after the date of randomisation, and those that are defined as a worsening of asthma that leads in at least one of the three criteria detailed in protocol Section 5.1.12 being fulfilled. This will include exacerbations where the eCRF exacerbation records a new/worsened symptom, requiring systemic corticosteroid intervention or hospitalization.

A summary table which counts subjects who have been incorrectly randomized and who received incorrect treatment will be presented.

Summary data will be presented in tabular format by treatment. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables for parametric data will be summarized by descriptive statistics including N, mean, standard deviation (SD), geometric mean, SD of log values, median, minimum and maximum. All data will be listed. Data listings will be sorted by treatment and subject number.

Measures of location (mean, geometric mean, median, minimum and maximum) will be reported to the same degree of precision as the raw data unless otherwise stated. Measures of spread (SD) will be reported to one further degree of precision.

Continuous descriptive statistics for the percent and absolute change from baseline will summarize N, mean, SD, median, minimum and maximum and will be based on raw data. Continuous descriptive statistics for the ratio will summarize N, geometric mean and SD of log values and will be based on log-transformed data. Primary and secondary efficacy variables will summarise the ratio, absolute and percent change, exploratory efficacy variables will summarise absolute and percent change, and non-efficacy summary statistics on the change from baseline will only present the absolute change.

The primary and secondary variables will be analysed using geometric means. Both the difference in number and the % change or ratio will be reported, but the statistical analysis will only be based on the ratio. All hypothesis testing will be reported using 2-sided tests. P-values will be rounded to 4 decimal places. No adjustment for multiplicity will be performed and nominal p-values will be reported.

For the efficacy analyses except PRO/ SNOT-20 data, if the value of the ratio of Week 12 to baseline is zero and both Week 12 and baseline are not missing, the ratio will be replaced, for the analysis of ratio only (including for descriptive statistics), by half the smallest observed ratio among the randomized subjects with non-zero values (both treatment arms). For the corresponding non descriptive analyses on the ratio, values of baseline equal to zero were replaced by half the smallest observed value among the subjects with non-zero for the calculation of the baseline logtransformed covariate,

For the efficacy analyses except PRO/ SNOT-20 data, if the baseline value is zero, the baseline will be replaced, for the analysis of ratio to baseline or percent change from baseline only (including for descriptive statistics), by half the smallest observed value among the randomized subjects with non-zero values and among all records (baseline and post baseline

for both treatment arms). If both the baseline and post-baseline record are zero, then the percent change is zero.

QQ plots of residuals of the primary and secondary efficacy analysis models (both on absolute change and log-transformed ratio) will be created.

#### 4.1.1 Sensitivity analyses

An ANCOVA will be done on raw data (no log-transformation) with the absolute change from baseline as response variable. The model will include treatment group as fixed effect and baseline value as a continuous covariate. No interaction terms will be included in the model.

To investigate the sensitivity to the Normality assumption in the Primary analysis, a non-parametric analysis of covariance (ANCOVA) model on the ranks of the absolute change from baseline at Week 12 (Visit 9) sensitivity analyses for the primary endpoint will be performed. Tied values will receive the mean values of the corresponding ranks.

A further sensitivity analysis of the ANCOVA based on ranks will be conducted based on the same model of the initial ANCOVA based on ranks, but using the ratio as response. The same replacement rule for ratio described above in section 4.1 will be applied for zero values.

It is likely that some biopsy specimens will not be evaluable. Although some subjects will have missing data for other reasons, it is envisaged that the invasive nature of the biopsy procedure will directly result in some missing biopsy outcomes. Such biopsy-related missing pattern is likely not to be informative about the potential outcome – that is, such data is likely to be missing at random (MAR). The following sensitivity analysis for the primary and the secondary endpoints will be used to explore the robustness of the analyses to assumptions about this missing biopsy data. This sensitivity analysis will take account of the potential difference between biopsy-related missingness (arguably MAR) and other sources of missing data. A subject will be counted as having biopsy-related missing outcome if the biopsy outcome is missing at Week 12, but other Week 12 data was collected for the subject. In the sensitivity analysis implemented by multiple imputation (MI), biopsy-related missingness will be imputed assuming MAR. All other missing values will be imputed with the “Dropout Reason-based Multiple Imputation (DRMI)”: Missing counts will be imputed differently depending on the reason for dropout; counts for subjects in the Tralokinumab arms who dropped out for a treatment related reason are imputed based on the expected event rate in the placebo arm ( $p_{T,2} = p_{P,1}$ ), whereas the remaining subjects who have dropped out are imputed assuming MAR. Treatment related reasons include (1) AEs, (2) Death (3) development of study specified reasons to stop active treatments and (4) severe non compliance.

The data will be log-transformed before the imputation process begins, and the ratio of each scheduled visit to baseline visit will be the variable of interest for imputation. The missing ratio at Week 12 (Visit 9) will be imputed using regression imputation (using MONOTONE REG option of SAS PROC MI). 100 imputations will be carried out, and a seed of 221014 will be used. The analysis of each of the imputed datasets will be as described for the primary

analysis in Section 4.2.4 and these will be combined using SAS procedure PROC MIANALYZE and results presented as per the primary analysis.

This approach assumes that no subject has a missing baseline result. If there are subjects with missing baseline results, a regression imputation will be used first, with missing baselines being replaced by their predicted values, given the other baseline covariates (apart from treatment group).

A further sensitivity analysis of the primary efficacy analysis will be done removing the subjects who have a subject with a baseline value=0 or a week 12=0.

As per section 3.1.4, week 12 records not collected within study days 78-99 will not be analyzed as part of the primary efficacy. A further sensitivity analysis of the primary efficacy will be done keeping the subjects with the week 12 records falling outside of the week 12 window.

## **4.2 Analysis methods**

### **4.2.1 Subject disposition, demography data and subjects characteristics**

Subject disposition will be summarized using the All subjects analysis set.

The number of enrolled subjects will be summarized. The number and percentage of subjects within each treatment group will be presented by the following categories; randomized, not randomized (and reason), received IP, did not receive IP (and reason), completed treatment, discontinued treatment (and reason), completed study, and discontinued study (including reason).

The number and percentage of subjects, who discontinued IP, but remained in the study will be presented by treatment group and will also be listed.

Demographic data such as age, gender, ethnicity and race will be summarized by treatment group for the FAS.

Various baseline characteristics will also be summarized by treatment for the FAS. These include medical, surgical and respiratory disease histories, asthma related events in the past 12 months, weight, height and BMI, use of nicotine (never/ former/ current), asthma duration (defined as date of informed consent – date of diagnosis), age at onset of asthma (defined as date of diagnosis – date of birth), asthma medications (using fluticasone as reference medication), the number of asthma exacerbations in the previous 12 months and number of asthma exacerbations requiring hospitalizations in the previous 12 months.

Medical and surgical histories will be summarized by MedDRA Preferred Term (PT) within the System Organ Class (SOC) level of MedDRA version 20.0.



#### 4.2.2 Prior and Concomitant Medications

The number and percentage of subjects receiving each medication (by Anatomical Therapeutic Chemical (ATC) classification system codes and generic name) will be presented by treatment for the FAS. Separate tables will be presented for all medications received during the following periods:

- Prior: Medications with a stop date  $\leq$  the first day of IP.
- Concomitant – during treatment: Medications that are still ongoing on the first day of IP and also medications with start date  $\geq$  the first day of IP and  $\leq$  the last day of IP + 2 weeks.
- Post –treatment: Medications that are still ongoing one day after (the last day of IP + 2 weeks) and also medications with start date  $>$  the last day of IP + 2 weeks and  $\leq$  Visit 11 (Week 26).

Tables for maintenance medications (started prior to and ongoing after the first day of IP) will be produced displaying the baseline total daily dose of ICS. The number of subjects using other maintenance asthma medications at baseline will also be summarized. In addition, the total number of days of systemic corticosteroid treatment associated with asthma exacerbations per subject from the first day of IP up to Week 12 will also be summarized.

A separate table will be presented for subjects who take disallowed concomitant medications. Disallowed medications will be defined using a combination of programming and a physician review (prior to database lock) of the unique combinations of ATC code classifications and generic terms captured.

Medications will be classified according to the AstraZeneca Drug Dictionary. Percentages will be calculated relative to the number of subjects in the FAS.

All medications will also be listed by subject for the FAS.

Data from subjects who discontinued IP but remain in the study, where possible and relevant, will be included in the appropriate medication summaries.

#### 4.2.3 Exposure and Compliance

Extent of exposure to IP is defined as the number of days between the start and the end dates of study therapy plus 14 days:

$$\text{Extent of exposure (days)} = (\text{Last dosing date} + 14 \text{ days}) - \text{First dosing date} + 1.$$

In addition, the total number of dosing occasions is calculated by summing the doses taken by the subject. The total number of dosing occasions expected is defined as:



*Total number of dosing occasions expected = number of visits during treatment phase the subject attended.*

Compliance is defined as:

*Compliance (%) = (Total number of dosing occasions/total number of dosing occasions expected) x 100*

Extent of exposure to IP, compliance and total number of dosing occasions will be summarized by treatment group, using the safety analysis set.

Compliance with the regularly scheduled ICS/LABA asthma inhaler as recorded in the daily diary will be summarized by each bi-weekly period and treatment group, together with the compliance of the use of the daily diary.

#### **4.2.4 Analysis of the primary variable**

All analyses of the primary endpoint will be based on the FAS.

The primary efficacy variable is the change, expressed as a ratio [Week 12 (Visit 9)/baseline] from baseline to Week 12 (Visit 9) in airway submucosal eosinophils and the primary analysis is to compare this change from baseline to Week 12 (Visit 9) for tralokinumab with placebo.

The primary efficacy variable will be evaluated through the hypothesis test:

$H_0$ : ratio (tralokinumab/placebo) equals 1 vs.  
 $H_1$ : ratio does not equal 1.

The null hypothesis ( $H_0$ ) is that the change in airway submucosal eosinophils at Week 12 on tralokinumab is equal to the corresponding change on placebo. The alternative hypothesis ( $H_1$ ) is that the change in airway submucosal eosinophils during the 12-week double-blind treatment period is different on tralokinumab compared with the change in airway submucosal eosinophils during the 12-week double-blind treatment period on placebo.

The change in airway submucosal eosinophils in the tralokinumab group will be compared to that seen in the placebo group using an ANCOVA model.

The response variable in the model will be change, on the log-scale (expressed as a ratio) in the number of airway submucosal eosinophils from baseline to Week 12 (Visit 9) [Week 12 (Visit 9)/baseline]. The model will include treatment group as fixed effect and baseline log value as a continuous covariate. No interaction terms will be included in the model. The analysis will be performed using log-transformed data. All group comparisons from ANCOVA model will be based on Type III sums of squares. Estimated geometric means (original scale) will be presented for each treatment group as well the ratio of geometric means for the comparison of tralokinumab versus placebo (tralokinumab/placebo) and corresponding 95% confidence interval (CI).

Available values at both baseline and Week 12 (Visit 9) are required for a subject to be included in the analysis.

Summary statistics for the absolute and percentage change from baseline to Week 12 (Visit 9) will also be presented.

Spaghetti plots will be presented for the primary efficacy variable (raw variable). A scatterplot will also be produced for baseline generation 4 wall area (WA) vs primary variable (using % change from baseline). The same spaghetti plots and scatter plots will be performed removing outliers. Outliers are defined as records below Q1 (first Quartile)-1.5\*IQR (Interquartile Range), and above Q3 (third Quartile) +1.5\*IQR. IQR is defined as Q3-Q1. Number of airway submucosal eosinophils and percentage change from baseline will also be listed.

#### **4.2.5 Analysis of secondary variables**

All secondary endpoints will be analyzed based on the FAS. Spaghetti plots will be presented for all secondary efficacy variable. A scatterplot will also be produced for baseline generation 4 WA vs ECP and separately MBP (Major Basic Protein), using % change from baseline.

##### **4.2.5.1 Blood eosinophil count**

**The secondary outcome variable blood eosinophil count is:** Change, expressed as a ratio [Week12 (Visit 9)/baseline], from baseline in the blood eosinophil count to Week 12 (Visit 9).

The change from baseline to Week 12 (Visit 9) in blood eosinophil count will be compared between tralokinumab and placebo using a mixed model for repeated measures (MMRM) with treatment group, logbaseline and visit as fixed effects. Treatment-by-visit interaction will also be included. The analysis will be performed by using log-transformed data on all post baseline visits during treatment phase.

The response variable will be the change, on the log-scale (expressed as a ratio) in blood eosinophil count from baseline to Week 12 (Visit 9) [Week 12 (Visit 9)/baseline]. A restricted maximum likelihood (REML) approach will be used. All subjects with a baseline blood eosinophil count in the FAS will be included in the analysis. An unstructured variance-covariance matrix will be used to model the within-subject errors. If the model fails to converge then a compound symmetric variance-covariance matrix will be used instead. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Estimated geometric means ratios (original scale) will be presented for each treatment group as well the ratio of geometric means ratios for the comparison of tralokinumab versus placebo (tralokinumab/placebo) and corresponding 95% CI.

An MMRM will also be done on raw data (no log-transformation) with the absolute change from baseline as response variable. The model will include treatment group as fixed effect baseline value, and visit as fixed effects. Treatment-by-visit interaction will also be included.

Summary statistics for the absolute change from baseline at all visits in blood eosinophil count will be presented by treatment group.

Blood eosinophil count and absolute change from baseline will also be listed.

#### 4.2.5.2 Differential sputum eosinophils

**The secondary outcome variable differential sputum eosinophils is:** Change, expressed as a ratio [Week12 (Visit 9)/baseline], from baseline in differential sputum eosinophils to Week 12 (Visit 9)

This will be analysed and summarised as described for blood eosinophil count in Section 4.2.5.1.

#### 4.2.5.3 Blood and sputum free ECP

**The secondary outcome variable blood and sputum free eosinophils cationic protein (ECP) is:** change, expressed as a ratio [Week12 (Visit 9)/baseline] in blood free ECP concentration from baseline to Week 12 (Visit 9); change, expressed as a ratio [Week12 (Visit 9)/baseline] in sputum free ECP concentration from baseline to Week 12 (Visit 9)

This will be analysed and summarised and described for the primary efficacy variable in Section 4.2.5.1.

#### 4.2.6 Analysis of exploratory variables

Change from baseline analysis will be performed for each exploratory variable detailed in Sections 3.2.3 and 3.3.1, and summarized using descriptive statistics and graphical displays (spaghetti plots, and scatter plots for some variables, see below).

Spirometry variables defined in Section 3.2.3.4 will also be summarised as per Section 4.2.5.1 for the descriptive statistics only – there won't be any MMRM. The analysis will be based on raw data – there won't be any log-transformation before the analysis.

##### 4.2.6.1 Scatter plots

The following scatter plots will be produced: baseline generation 4 WA% versus:

- FEV1 (absolute change from baseline)
- FEV1 (% change from baseline)
- AHR PD20 (baseline value)
- AHR PD20 (absolute change from baseline)
- AHR PD20 (% change from baseline)
- Generation 4 CT Lumen area, Airway  $LA_{\text{Generation 4}}$  (% change from baseline)
- Generation 4 CT Wall area, Airway  $WA_{\text{Generation 4}}$  (% change from baseline)
- Generation 4 CT WA%, Airway  $WAF_{\text{Generation 4}}$  (% change from baseline)
- Generation 5CT Lumen area, Airway  $LA_{\text{Generation 5}}$  (% change from baseline)
- Generation 5CT Wall area, Airway  $WA_{\text{Generation 5}}$  (absolute change from baseline)
- Generation 5CT WA% Airway  $WAF_{\text{Generation 5}}$  (% change from baseline)

#### **4.2.6.2 Subgroup analyses**

The consistency of treatment effect on FEV<sub>1</sub> and Airway LA Generation 4 (% change from baseline) parameters across different subgroups (high. vs. low baseline Generation 4WA% (median cut-off)) will be explored using descriptive statistics for continuous data based on the FAS.

#### **4.2.6.3 Exacerbation**

Exacerbations will be listed only.

#### **4.2.7 Serum Biomarkers and immunology**

Serum biomarkers and IgE will be summarised, for each parameter, by visit and treatment group, using descriptive statistics for continuous data.

The serum biomarkers include, but are not limited to, periostin; DPP4.

#### **4.2.8 Analysis diary data variable(s)**

All diary data parameters will be summarized on the FAS using the methodology described in section 4.2.5.1 for the descriptive statistics only – there won't be any MMRM. The diary data analysis will be based on raw data – there will not be any log-transformation before the analysis.

##### **4.2.8.1 Asthma symptoms**

**The key secondary outcome variable:** Change from baseline in bi-weekly mean daily asthma symptom total score (combined daytime and night-time score as captured in the Asthma Daily Diary).

The absolute change from baseline in bi-weekly means (daily asthma symptom total score, daytime score, and night-time score) at Week 12 will each be summarized as described in Section 4.2.5.1 for the descriptive statistics only – there won't be any MMRM.

The proportion of asthma symptom-free days up to Week 12 will also be summarized.

##### **4.2.8.2 ACQ-6 defined asthma control**

Percent change in mean score from baseline for ACQ-6 (and each of the individual questions) will be summarized as described in Section 4.2.5.1 for the descriptive statistics only – there won't be any MMRM.

The number and percentage of subjects achieving mean ACQ-6  $\leq 0.75$ ,  $0.75 < \text{mean ACQ-6} < 1.5$  and mean ACQ-6 of  $\geq 1.5$  at Week 12 will be summarized by treatment. Additionally, the number and percentage of subjects achieving an improvement, no change, or deterioration as per Section 3.3.1.5, will also be summarized by treatment.

#### **4.2.8.3 Nights with awakening due to asthma**

The change from baseline in the bi-weekly mean number (percentage) of nights with awakening due to asthma that required rescue medication will be summarized as described in Section 4.2.5.1 for the descriptive statistics only – there won't be any MMRM.

#### **4.2.8.4 Rescue medication use**

The change from baseline in bi-weekly mean rescue medication use will be summarized as described in Section 4.2.5.1 for the descriptive statistics only – there won't be any MMRM.

The number and percentage of subjects within each treatment group who received rescue medication will be summarized by each bi-weekly period.

#### **4.2.8.5 Home PEF (morning and evening)**

The percent change from baseline in bi-weekly mean morning and evening PEF will each be summarized as described in Section 4.2.5.1 for the descriptive statistics only – there won't be any MMRM.

#### **4.2.8.6 SNOT-20**

The change from baseline in SNOT-20 will each be summarized as described in Section 4.2.5.1. Percentage of subjects answering "most important" in SNOT-20 questionnaire will be summarized by treatment group and planned visit.

### **4.2.9 Safety and tolerability**

All safety variables will be summarized using the safety analysis set and data presented according to treatment randomized.

#### **4.2.9.1 Adverse events (AEs)**

AEs will be summarized separately for the treatment and study periods. AEs occurring during the run-in period, or occurring post-treatment (as per the definition in Section 3.4.1) will be listed, but not summarized separately.

An overall summary table will be produced showing the number and percentage of subjects with at least 1 AE in any of the following categories; AEs, SAEs, deaths due to AE, AEs causing discontinuation of IP (DAEs), and other significant AEs (OAEs). OAEs will be defined following medical review of system organ classes/preferred terms after unblinding of the data. The total number of AEs in the different AE categories in terms of AE counts will also be presented (ie, accounting for multiple occurrences of the same event in a subject).

AEs will be summarized by SOC and PT assigned to the event using MedDRA version 20.0. For each PT, the number and percentage of subjects reporting at least one occurrence will be presented ie, for a subject multiple occurrences of an AE will only be counted once.

AEs (by SOC and PT) will be summarized by causality and maximum intensity. If a subject reports multiple occurrences of the same AE, the maximum intensity will be taken as the

highest recorded maximum intensity (the order being mild, moderate, and severe). AEs with missing intensity will not be outputted in this table.

The following will also be summarized by SOC and PT

SAEs

OAEs in the category of safety topics of special attention

DAEs

DAEs causally related to IP

SAEs leading to discontinuation of IP

Most common AE's (frequency of >3%) (by PT only)

Deaths

Severe Infections

Severe infections will be identified as AEs that have been entered into the infection modules in the eCRF (INFDI, INFRF and INFSS).

Injection site reactions will be reported by preferred term for the treatment period, summarized by treatment group.

The approach to identifying anaphylaxis/hypersensitivity AEs occurring within 3 days of IP administration is described in a separate charter. Those identified AEs meeting the criteria described in this charter will be summarized by preferred term and treatment group for the treatment period and study period.

Subjects experiencing a severe infection are defined as having an AE which met one of the following:

- life-threatening,
- requiring hospitalisation,
- requiring treatment with antiviral medications, intravenous antibiotics or medications for helminth parasitic infections,
- permanent discontinuation of study drug.

Severe infections will be summarized by MedDRA high level group term, high level term and preferred term by treatment group for the treatment period and study period.

The rate of AEs per person-years at risk, calculated as (number of subjects reporting AE)/(total time at risk of AE), will also be reported. Rates will typically be expressed in terms of events per 100 subject-years. Total time at risk will be defined as the date of last visit in the 12-week treatment period – date of randomization +1.

Separate listings of subjects with AEs, SAEs, death due to AE, discontinuations due to AEs, or severe infections will be presented.

#### 4.2.9.2 Laboratory data

All continuous laboratory parameters will be summarized by absolute value at each visit by treatment group, together with the corresponding changes from baseline. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD. Mean changes from baseline over time will also be plotted by treatment group.

Central laboratory reference ranges will be used for the identification of individual clinically important abnormalities, and a shift table will be produced for each laboratory parameter to display low, normal, high, and missing values. The shift tables will present baseline and maximum/minimum on-treatment value, as applicable for each parameter.

Shift plots showing each individual subject's laboratory value at baseline and at maximum/minimum will be produced for each continuous laboratory variable. If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at other time points then shift plots of these data may be produced. A diagonal line indicating no change, and horizontal and vertical reference lines indicating the limits of the reference ranges will also be displayed on the shift plots.

Data for subjects who have treatment-emergent changes outside the predefined criteria will be presented. This data presentation will include all visits for this subset of subjects. A change is treatment-emergent if it occurred during treatment, using the same definition as in Section 3.4.1.

The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Frequencies of clinically noteworthy values (using reference ranges) occurring during the clinical study will also be given.

In order to identify potential Hy's Law cases, maximum post baseline TBL will be plotted against maximum post baseline ALT, expressed as multiples of ULN. This plot will be repeated to show maximum post baseline TBL against maximum post baseline AST, expressed as multiples of ULN. These plots will be produced on a log scale and reference lines will be included at 2xULN for TBL and at 3xULN for ALT/AST.

For all subjects who meet the biochemical criteria for Hy's law (potential Hy's Law), a Subject Safety Narrative will be produced, and the relevant laboratory parameters will be tabulated showing all visits for these subjects. Subjects with elevated ALT or AST, and elevated TBL, at any time may be explored further graphically using individual subject profile plots.

For urinalysis data, a shift table will be generated to present changes from baseline to last observation in the on-treatment period (as defined in Section 3.4.1). The number of subjects with treatment-emergent changes will also be summarized. Here, treatment-emergent changes are defined as None/Trace at baseline to Positive at any visit after baseline.

Any data outside the central laboratory reference ranges will be explicitly noted on the listings that are produced.



#### **4.2.9.3 ECGs**

The Investigator's assessment of the 12-lead ECG (normal or abnormal) will be listed for all subjects, along with detailing whether any abnormalities were clinically significant or not.

The number and percentage of subjects with clinically significant abnormal ECGs will be summarized by treatment group and visit.

#### **4.2.9.4 Physical Examination**

Shift tables (normal, abnormal (same as Visit 1, new or aggravated) of Visit 1 versus last observation during treatment will be generated, presenting the assessment for each component of the complete physical examination separately.

A similar shift table (normal, abnormal) of baseline (typically Visit 3) versus the last observation during treatment will also be generated.

Listings of results will be produced, including the date of assessments of the brief physical exam.

#### **4.2.9.5 Vital Signs**

All vital signs parameters will be summarized by absolute value at each visit by treatment group, together with the corresponding changes from baseline. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD.

AstraZeneca defined reference ranges will be used for the identification of individual abnormalities, and a shift table will be produced for each vital signs parameter to display low, normal, high, and missing values. The shift tables will present baseline and maximum/minimum during treatment value, as applicable for each parameter.

Shift plots showing each individual subject's vital signs value at baseline and at maximum/minimum will be produced for each continuous vital signs parameter.

A shift table will be generated to present changes from baseline to last observation during study.

Data for subjects who have treatment-emergent changes outside the predefined criteria will be presented, using AstraZeneca clinically important change criteria. This data presentation will include all visits for each parameter with treatment-emergent changes for this subset of subjects. A change is treatment-emergent if it occurred during treatment, using the same definition as in Section 3.4.1.

All recorded vital signs data will be listed.

#### **4.2.9.6 Pregnancy test**

Number and percentage of subjects with positive urine pregnancy test will be summarised by visit.



#### **4.2.9.7 Analysis of Immunogenicity variables**

All analyses on Immunogenicity variables will be based on the safety analysis set. The overall ADA status for each subject will also be classified and summarized by treatment group. A subject will be categorised as overall ADA positive, if they have a positive ADA status at any point during the study (including baseline), otherwise a subject will be overall ADA negative. The association of overall ADA status across the study with AEs/SAEs will be evaluated. The following ADA results may be evaluated as proportion of subjects in cohorts together with corresponding titer summaries.

- Subjects who are ADA positive at any time (including baseline).
- Subjects who are ADA positive at baseline only.
- Subjects who are ADA positive at baseline and positive in at least one post baseline measurement.
- Subjects who are positive at baseline regardless of post-baseline result.
- Subjects who are ADA positive post-baseline.
- Subjects who are ADA positive post-baseline and ADA negative at baseline.
- Subjects who are persistently positive; persistently positive is defined as at least 2 post-baseline ADA positive measurements ( $\geq 16$  weeks apart) or an ADA positive result at the last available assessment..
- Proportion of subjects who are transiently positive; transiently positive is defined as at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.

For ADA, all subjects with titer information will be shown in the data listing, by dose level.

#### **4.2.10 Analysis of pharmacokinetics**

All analyses of PK variables will be based on the PK analysis set.

Due to the limited sampling schedule, the PK assessment will be based on the observed pre-dose serum trough concentrations,  $C_{\text{trough}}$ . This will be summarised by visit.

The lower limit of quantification (LLOQ) of tralokinumab in serum will be 0.100  $\mu\text{g/mL}$ .

Tralokinumab serum concentrations will also be listed.

## **5. INTERIM ANALYSES**

No interim analysis is planned for this study.

## 6. CHANGES OF ANALYSIS FROM PROTOCOL

A number of clarifications and minor corrections have been made and are listed below:

- Section 3.4.3/4.2.9.2: due to the way the data is collected on the eCRF, the urinalysis categories have been updated to negative, trace or positive.
- The presentation of asthma exacerbations is not detailed in the protocol. This has been added as an exploratory variable (Section 1.1.4) and some text detailing summaries that will be provided have been included. In addition, a start and end date definition of an exacerbation has also been added.
- Section 3.3.1.5: Categorisation of Improved/ No Change/ Deterioration has been re-labelled as ACQ-6 Response to be distinct from ACQ-6 Responder which is Yes or No.
- Section 1.1.4 p.15: The analysis is now calculate the change from baseline up to Week 12 in fractional exhaled nitric oxide (FE<sub>NO</sub>)
- Section 3.1.1: Baseline for Asthma Daily Diary variables will be, for each variable, the average of all the daily records within the 14 days prior to randomization
- Section 3.2.3.1 to Section 3.2.3.3: ratios will also be calculated for sputum, serum, large and small airways remodelling variables
- Section 3.3.1.3: Bi-weekly mean number of nights is expressed as a percentage
- Section 3.4.1 and 4.2.2: increased follow-up period to 20 weeks
- Section 1.1.4 and 3.2.3.2, 3.2.3.3: The three types of change from baseline analyses (absolute, percent, ratio) will be performed for all exploratory endpoints.
- Section 3.2.3.1: Removed analysis of soluble biomarkers, serum biomarker, nasosorption biomarkers, airway epithelial gene expression, airway volume and resistance based on FRI, effect of Tralo on RNA.
- Removed references to sub-sub segmental as team will be combining sub-segmental and sub-sub-segmental analyses together.
- SNOT-20 is coming from RAVE, and not from the e-diary data.
- The change in sputum eosinophils as percentage number of inflammatory cells won't be analysed (this was a supportive secondary outcome measure added in protocol amendment 2).
- MMRM only performed on secondary efficacy; not on efficacy

- Section 2.1.3: The definition of PK analysis set has been updated to include subjects in FAS who received tralokinumab and had blood samples obtained for PK.
- Section 3.4.2: The OAEs have been updated to safety topics of special attention
- Section 4.1: Under general principles, the p-values rounding has been updated from 3 to 4 decimal places (reference CSP section: 8.5).
- Section 4.1: Clarified analyses of percent change and ratio when baseline and / or post-baseline=0.
- Added further sensitivity analysis on sponsor request.

## 7. REFERENCES

**[1] Michael O’Kelly, Bohdana Ratitch.**

Clinical trials with missing data A guide for practitioners. Wiley, 2014.

**[2] Koch et al 1998**

Koch GG, Tangen CM, Jung J-W, Amara IA. Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and nonparametric strategies for addressing them. *Statistics in Medicine* 1998;17:1863-92.

**[3] A Multicentre, Randomized, Double-blind, Parallel Group, Placebo Controlled, 12-Week, Phase 2 Study to Evaluate the Effect of Tralokinumab on Airway Inflammation in Adults with Asthma Inadequately Controlled on Inhaled Corticosteroid (MESOS).** Final Protocol version 1.0, 26 February 2015.