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**Statistical Analysis Plan**

Study Code D2210C00013

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**A Multicentre, Randomized, Double-blind, Parallel Group, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Tralokinumab in Reducing Oral Corticosteroid Use in Adults and Adolescents with Oral Corticosteroid dependant Asthma (TROPOS)**

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Study Statistician

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12 Sept 2017  
Date

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Global Product Statistician

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12<sup>th</sup> Sept 2017  
Date

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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
AAER	Annual Asthma Exacerbation Rate
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AQLQ(S) +12	Standardised Asthma Quality of Life Questionnaire for 12 Years and Older
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BD	Bronchodilator
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DAE	Discontinuation of Investigational Product due to Adverse Event
dECG	Digital Electrocardiogram
DPP-4	Dipeptidyl Peptidase-4
eCRF	Electronic Case Report Form
ER	Emergency Room
EOS	End of Study
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome device
EQ-5D-5L	European Quality of Life - 5 Dimensions - 5 Levels
FEF <sub>25-75%</sub>	Forced Expiratory Flow between 25% and 75% of the Forced Vital Capacity
FE <sub>NO</sub>	Fractional Exhaled Nitric Oxide
FEV <sub>1</sub>	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GGT	S-Gamma-glutamyl transpeptidase
ICS	Inhaled Corticosteroids



<b>Abbreviation or special term</b>	<b>Explanation</b>
IgE	Immunoglobulin E
IL-13	Interleukin-13
IP	Investigational Product
ITT	Intent-to-Treat
LABA	Long-Acting $\beta_2$ -Agonist
MACE	Major adverse cardiac events
LS	Least Squares
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing not at Random
nAb	Neutralizing Antibodies
NC	Not Calculable
NQ	Non-quantifiable
OAE	Other Significant Adverse Event
OCS	Oral Corticosteroids
PEF	Peak Expiratory Flow
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcome
PT	Preferred Term
Q2W	Every 2 Weeks
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
UC	Urgent Care
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WPAI+CIQ	Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire

## AMENDMENT HISTORY

<b>Date</b>	<b>Brief description of change</b>
22 Jul 2016	Update to create consistency between Stratos1 and 2
25 May 2016	Update to maintain alignment with Stratos 1 and 2, include analyses from Zonda (benralizumab), and include FeNO as biomarker.
31 August 2016	Update of biomarker presentation strategy. Elevation of asthma exacerbation to secondary endpoint. Addition of possible tipping point analysis. Change of secondary analysis from CMH to logistic regression to accommodate interaction with biomarker.

## 1. STUDY DETAILS

This is the statistical analysis plan (SAP) for study D2210C00013. 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 compared to placebo in reducing the prescribed, oral corticosteroid (OCS) maintenance dose in adult and adolescent subjects in the primary population (Section 4.1.1) with asthma requiring chronic treatment with maintenance OCS in addition to inhaled corticosteroid (ICS) plus long-acting $\beta_2$ -agonist (LABA)	<p><b>Primary outcome variable:</b> Percent change from baseline in the daily, average, oral OCS dose at Week 40 post randomization while not losing asthma control</p> <p><b>Primary outcome measure:</b> Percent difference vs. placebo at Week 40 post randomization</p>

#### 1.1.2 Secondary objectives

Secondary Objectives:	Outcome Measures:
To evaluate the effect of tralokinumab compared to placebo on the proportion of subjects with the prescribed, OCS dose $\leq 5$ mg in adult and adolescent subjects in the primary population (Section 4.1.1) with asthma requiring chronic treatment with maintenance OCS in addition to inhaled corticosteroid plus LABA	<p><b>Outcome variable:</b> Proportion of subjects with final daily average OCS dose <math>\leq 5</math> mg.</p> <p><b>Outcome measure:</b> Difference vs. placebo at Week 40 post randomization.</p>
To evaluate the effect of tralokinumab compared to placebo on the proportion of subjects in the primary population (Section 4.1.1) with at least 50% reduction in their prescribed, OCS maintenance dose in adult and adolescent subjects with asthma requiring chronic treatment with maintenance OCS in addition to ICS plus LABA	<p><b>Outcome variable:</b> Proportion of subjects with <math>\geq 50\%</math> reduction in average daily OCS dose.</p> <p><b>Outcome measure:</b> Difference vs. placebo at Week 40 post randomization.</p>

<p>To evaluate the effect of tralokinumab compared with placebo on asthma exacerbations in adult and adolescent subjects in the primary population (Section 4.1.1) with asthma requiring chronic treatment with maintenance OCS in addition to ICS plus LABA</p>	<p><b>Outcome variable:</b> The annualised asthma exacerbation rate (AAER) up to Week 40.</p> <p><b>Outcome measure:</b> Asthma exacerbation rate reduction</p>
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### 1.1.3 Safety objective

<b>Objective:</b>	<b>Outcome Measures:</b>
<p>To evaluate the safety and tolerability of tralokinumab</p>	<ul style="list-style-type: none"> <li>• Adverse Events (AE) /Serious Adverse Events (SAE)</li> <li>• Vital signs</li> <li>• Digital electrocardiograms (dECG)</li> <li>• Clinical chemistry/haematology/urinalysis</li> <li>• Physical examinations</li> </ul>

### 1.1.4 Exploratory objectives

<b>Objectives:</b>	<b>Outcome Measures:</b>
<p>To evaluate the effect of tralokinumab versus placebo in overall oral corticosteroid exposure</p>	<p>Overall OCS exposure measured by the area under the dose curve.</p>
<p>To evaluate the effect of tralokinumab versus placebo in the proportion of subjects that have decreased their daily average prescribed, OCS dose</p>	<p>Proportion of subjects reducing their daily average OCS dose classified by: 100% reduction (no OCS), <math>\geq 90\%</math> to <math>&lt; 100\%</math> reduction, <math>\geq 75\%</math> to <math>&lt; 90\%</math> reduction, <math>\geq 50\%</math> to <math>&lt; 75\%</math> reduction, <math>&gt; 0\%</math> to <math>&lt; 50\%</math> reduction, no change in average OCS dose, increased average OCS dose.</p>
<p>To evaluate the effect of tralokinumab compared with placebo on lung function</p>	<p><b>Outcome variables:</b> Percent change from baseline in pre-bronchodilator (BD) forced expiratory volume in 1 second (FEV<sub>1</sub>), Forced Vital Capacity (FVC) and Forced Expiratory Flow between 25% and 75% of the Forced Vital Capacity (FEF<sub>25-75%</sub>)</p> <p><b>Outcome measure:</b> Percent difference vs. placebo at Week 12 and 40</p>

<p>To evaluate the effect of tralokinumab compared with placebo on asthma symptoms and other asthma control metrics</p>	<p><b>Outcome variables:</b></p> <ul style="list-style-type: none"> <li>- Change from baseline in bi-weekly mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily Diary).</li> <li>- Change from baseline in rescue medication use.</li> <li>- Change from baseline in home peak expiratory flow (morning and evening) (PEF).</li> <li>- Change from baseline in the number of night-time awakening due to asthma.</li> <li>- Change from baseline in Asthma Control Questionnaire 6 (ACQ-6).</li> </ul> <p><b>Outcome measure:</b> Mean difference vs. placebo at Week 12 and Week 40</p>
<p>To evaluate the effect of tralokinumab compared with placebo with regards to asthma specific health-related quality of life</p>	<p><b>Outcome variable:</b> Change from baseline in Standardised Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(S)+12) total score.</p> <p><b>Outcome measure:</b> Mean difference vs. placebo at Week 12 and Week 40.</p>
<p>To evaluate the effect of tralokinumab compared with placebo with regards to health related quality of life.</p>	<p><b>Outcome variable:</b> European Quality of Life 5 Dimension 5 Level Questionnaire (EQ-5D-5L)</p> <p><b>Outcome measure:</b> Mean difference vs. placebo at Week 12 and Week 40 (Visual Analogue Scale (VAS))</p>
<p>To evaluate the effect of tralokinumab compared with placebo with regards to health care resource utilization and productivity loss due to asthma</p>	<p><b>Outcome variables:</b></p> <ul style="list-style-type: none"> <li>- Asthma specific resource utilization (e.g., unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications)</li> <li>- Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire (WPAI+CIQ) scores</li> </ul> <p><b>Outcome measure:</b> Mean difference vs. placebo at Week 12 and Week 40</p>
<p>To evaluate the pharmacokinetics (PK) and immunogenicity of tralokinumab</p>	<p><b>Outcome variables:</b></p> <ul style="list-style-type: none"> <li>- PK parameters: <math>C_{trough}</math></li> <li>- Immunogenicity outcome variables: incidence rate of positive anti-drug antibodies and characterization of their neutralizing potential</li> </ul>

<p>To evaluate the change from baseline of biomarkers that may be associated with upregulation of interleukin-13 (IL-13)</p>	<p>Biomarkers will include:</p> <ul style="list-style-type: none"> <li>- Periostin</li> <li>- Dipeptidyl peptidase-4 (DPP-4)</li> <li>- Blood eosinophils</li> <li>- Total serum Immunoglobulin E (IgE)</li> <li>- Fractional exhaled nitric oxide (FEno)</li> </ul> <p>Other specific blood biomarkers may also be analyzed.</p>
<p>To evaluate the relationship between baseline biomarkers and the effect of tralokinumab on OCS dose reduction and clinical efficacy</p>	
<p>To evaluate the impact of OCS optimization on biomarkers</p>	

## 1.2 Study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate the efficacy and safety of a fixed 300 mg dose of tralokinumab administered subcutaneously every 2 weeks (Q2W) in adult and adolescent subjects with OCS dependent asthma.

Approximately 120 subjects will be randomized to tralokinumab or placebo (1:1 ratio) globally from about 50 centers. Subjects will be stratified at randomization by age group (adults versus adolescents) and the adults will be further stratified by the baseline OCS dose ( $\leq 10$  mg versus  $> 10$  mg prednisone or prednisolone).

After the initial enrolment (Visit 1) and confirmation of entry criteria subjects will, depending on their recent asthma and OCS medication history, enter either:

- a 2-week run-in period (if there has been documented failure of OCS dose reduction within 6 months prior to Visit 1 and after discussion with the sponsor study physician) or
- a 2-week run-in period plus an 8-week optimization period to establish a minimum effective dose of the prescribed OCS (established by dose titration every two weeks).

The criteria for the adjustment of the OCS dose are in Section 5.1.2 of the CSP.

Once subjects have completed the run-in period or run-in/optimization period, (reached their minimum effective dose of OCS and have remained stable on this dose for 2 weeks) they will be randomized to a 40-week treatment period.

The total treatment period of 40 weeks consists of three phases: an initial 12 week induction phase needed to ensure maximal effect on FEV<sub>1</sub>; a 20 week OCS dose reduction phase to reach the lowest possible dose based on the titration schedule (CSP Table 4) and a maintenance phase to demonstrate that asthma control is maintained after achieving the lowest OCS dose.

The details of the three phases are listed below:

- Induction phase (12 weeks) – from Week 0 up to Week 12 where subjects should remain on their optimized OCS dose
- OCS reduction phase (20 weeks) – from Week 12 up to Week 32, OCS dose reduction can be started at Week 12 with the possibility of dose titration every 4 weeks. (for dose reduction criteria see CSP Section 5.1.2)
- Maintenance phase (8 weeks) – after the Week 32 visit to Week 40, subjects should remain on the OCS dose reached at Week 32 or remain on complete OCS elimination.

The last dose of tralokinumab or placebo will be given at Week 38 with end of treatment visit at Week 40.

Subjects will be maintained on their currently prescribed ICS/ LABA therapy and any additional asthma controller medications, without changes, from enrolment throughout the run-in/optimization and treatment periods.

Should the subject need to discontinue investigational product (IP) for any reason, every effort should be taken for the subject to be followed-up according to one of three options:

1. Ideally the subject should return for all regular clinic visits and perform all scheduled assessments until he/she completes a total of 40 weeks in the study, or
2. The subject will be offered to be followed up on a monthly basis via telephone calls while continuing eDiary completion, until the subject completes 40 weeks in the study (no further procedures will be performed) or,
3. If the subject cannot comply or does not wish to comply with the options above, the Investigator will only contact the subject at 40 weeks post randomization. No study assessments will be performed prior to this contact

The key elements to be collected at these follow up visits or telephone contacts for options 2 and 3 are AEs/SAEs, changes in concomitant medications, and asthma exacerbation information.

Follow up visits will be performed at Week 44 and Week 54.

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

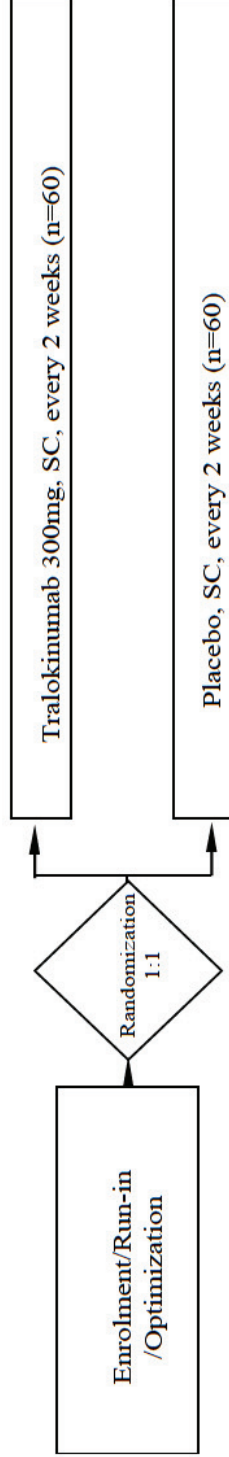
Results of study D2210C00007 (STRATOS 1) indicated that the benefit of Tralokinumab may be restricted to those patients with high levels of FeNO at baseline. Given that TROPOS had already completed recruitment (N = 140) and that the distribution of FeNO values at baseline in TROPOS is unknown, the primary population chosen will be determined by observed distribution of the biomarker in TROPOS. If at least 50% of the TROPOS sample have FeNO

$\geq 37$  ppb, then the primary population for testing primary and secondary endpoints will be the subpopulation of subjects with FeNO  $\geq 37$  ppb. Otherwise, if at least 50% of the TROPOS sample have FeNO  $\geq 30$  ppb the primary population will be the subpopulation of subjects with FeNO  $\geq 30$  ppb. Otherwise, the primary population will be the all-comers population. This is to ensure that the primary analyses will be performed on a sufficient number of subjects.



**Figure 1 Study flow chart**

Visit 1	Visit 2 – Visit 5**	Visit 6	40-Week, Double-Blind, Randomized, Treatment Period Visits 7-25		Visit 26	Visits 27, 28
Enrolment/ Run-in Week –10*	Optimization Weeks –8 to 0	Week 0	Induction Phase Weeks 0 up to 12	OCS Dose Reduction Phase Weeks 12 up to 32	EOT	FU Weeks 44, 54
				Maintenance Phase Weeks 32-40		



\*Visit 1 will be Week -2. For subjects not undergoing dose optimization

\*\*Visit 2 –Visit 5 to be completed for subjects that do not have a documented failure of OCS dose reduction within 6 months prior to Visit 1.

### 1.3 Number of subjects

The TROPOS study was originally sized for a primary comparison in the all-comer population assuming a difference in mean percentage reduction of OCS dose (primary) between the active and placebo of 50% in the full studied all-subject population. Based on previous studies of OCS reduction, a standard deviation of 80% was used. Assuming a Type I error rate of 5% and at least 90% power, the sample size required was estimated to at least 55 evaluable subjects per treatment group.

Subsequent to full recruitment of TROPOS and following STRATOS 1 results, the targeted difference has been reassessed. It is now assumed that the treatment benefit of tralokinumab may be related to biomarker level.

If the observed prevalence of the FeNO High subgroup is at least 50%, that subgroup will be used as the primary population for statistical testing. Otherwise, if the observed combined prevalence of the FeNO High and FeNO Mid subgroups is at least 50%, the combined FeNO Mid/High subgroup will be used as the primary population. Otherwise, the all-comers population will be used as the primary population.

With TROPOS fully recruited (N=140) as originally planned, the expectation that the treatment effect is 50% OCS reduction in the FeNO High subgroup, 30% OCS reduction in the FeNO Mid subgroup and a conservative 0% OCS reduction in the FeNO Low subgroup, an estimate of 80% for the standard deviation of OCS reduction responses, and a Type I error rate of 5% then:

- If FeNO High is the primary population (minimum 50% prevalence of FeNO High), at least 35 subjects per arm will provide at least 73% power. The power for this scenario increases to 96% if all 70 randomized subjects per arm are in the FeNO High subgroup.
- If FeNO Mid + High is the primary population (minimum 50% prevalence of FeNO Mid+High), the power ranges from 34% to 83%. The minimum power occurs when exactly 35 subjects per arm come exclusively from the FeNO Mid subgroup and represent a population with 30% treatment effect. The maximum power occurs when all 70 randomized subjects per arm are in the FeNO Mid+High subgroup without enough FeNO High subjects for the FeNO High subgroup to be chosen as the primary population (34 FeNO High and 36 FeNO Mid)
- If the all-comers population is the primary population, 70 subjects per arm provide 2.5% to 44% power. The maximum power occurs at the maximum hypothesized treatment effect in this group: 24% OCS reduction, assuming 34 subjects per arm are FeNO High and 36 subjects per arm are FeNO Low.

## 2. ANALYSIS SETS

### 2.1 Definition of analysis sets

#### 2.1.1 All subjects analysis set

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

**Biomarker (FeNO) populations:** The FeNO High population is defined as subjects in the all subject population with a baseline  $FE_{NO} \geq 37$  ppb. The FeNO Mid population is defined as subjects in the all subject population with a baseline  $FE_{NO} \geq 30$  ppb and  $< 37$  ppb. These cut-offs are defined based on results from the STRATOS 1 (D2210C00007) study. The FeNO Low population is defined as those subjects in the all subject population with a baseline  $FE_{NO} < 30$  ppb. Presentations may combine FeNO Low+Mid or FeNO Mid+High.

For the reporting of efficacy data, the FeNO High, Mid, and Low populations will be subsets of the Full analysis set (FAS). For the reporting of safety data, the FeNO High, Mid, and Low populations will be subsets of the Safety analysis set. Any subjects with missing  $FE_{NO}$  data which prevents determining their FeNO subgroup will not be included in any of the FeNO populations. If there are more than 10% of subjects from the all subjects population excluded from the biomarker positive and negative populations, additional summaries may be provided using this subset of “unknown” biomarker status.

#### 2.1.2 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, according to the ITT principle. 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.

**FAS – FeNO High:** All subjects in the FAS with a baseline  $FE_{NO} \geq 37$  ppb

**FAS – FeNO Mid:** All subjects in the FAS with a baseline  $FE_{NO} \geq 30$  ppb and  $< 37$  ppb

**FAS – FeNO Low:** All subjects in the FAS with a baseline  $FE_{NO} < 30$  ppb

#### 2.1.3 Safety analysis set

**Safety analysis set (Safety):** All subjects who receive 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 will be classified as active. Any deviations from the randomized treatment assignment will be listed and considered when interpreting the safety data. All safety summaries and anti-drug antibodies (ADA) analysis and summaries will be based on this analysis set.

**Safety – FeNO High:** All subjects in the Safety analysis set with a baseline FE<sub>NO</sub> ≥ 37 ppb

**Safety – FeNO Mid:** All subjects in the Safety analysis set with a baseline FE<sub>NO</sub> ≥ 30 ppb and < 37 ppb

**Safety – FeNO Low:** All subjects in the Safety analysis set with a baseline FE<sub>NO</sub> < 30 ppb

#### 2.1.4 PK analysis set

**PK analysis set:** All subjects in the FAS 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 PK analysis set. All PK summaries will be based on this analysis set.

#### 2.1.5 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 clinical study report (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 (listing in Table 1, for any reason, unless otherwise specified) during the randomized treatment period.

**Table 1 Disallowed medications considered to be important protocol deviations**

Medication Details	Anatomical Therapeutic Chemical (ATC) code(s)	Preferred term <sup>a</sup> (if applicable)
Zileuton		ZILEUTON
Live Attenuated Vaccines <sup>b</sup>	J07BD , J07BF, J07BJ, J07BK, V04CF, J07AP, J06BB, J07BB J07BH J07BL	

<b>Medication Details</b>	<b>Anatomical Therapeutic Chemical (ATC) code(s)</b>	<b>Preferred term<sup>a</sup> (if applicable)</b>
Any immunomodulators or immunosuppressives	L04AX, L04AD, L01BA , L04AX	
Blood products or immunoglobulin therapy	J06BC, B05A, R03DX	
Any marketed or investigational biologic treatment	R03DX, L04AC	OMALIZUMAB MEPOLIZUMAB RESLIZUMAB
Roflumilast (Daxas/ Daliresp)	R03DX	ROFLUMILAST
Oral or ophthalmic $\beta$ - adrenergic antagonist <sup>b</sup>	S01ED, C07AA, C07AG	
Herbal remedies <sup>b</sup>	R05CA	

<sup>a</sup> Preferred term will be used in combination with the ATC codes to identify medications

<sup>b</sup> Additional physicians review is required to identify these medications correctly. They will be programmatically isolated for review using the ATC codes.

<sup>c</sup> Additional physicians review is required to identify these medications correctly. They will be programmatically isolated for review using the ATC codes and duration. Only medications with a duration of  $\geq 30$  days will be flagged for review, Temporary use ( $< 30$  days) of systemic corticosteroids for treatment of asthma exacerbations or other acute conditions is allowed.

- Subjects who receive the incorrect IP or study dose at any time during the 40 week treatment period
- Subjects who develop withdrawal/discontinuation of IP criteria (CSP Section 3.9.1) during the study but were not withdrawn/discontinued from IP.
- Subjects for whom the protocol-defined post-baseline OCS dose titration procedures are not followed and which could have impacted the final OCS dose.
  - Subjects who do not meet the down-titration criteria but are down-titrated.
  - Subjects who meet the down-titration criteria but are not down-titrated.

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

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

#### **3.1 General Definitions**

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

In general, the last measurement on or prior to the date of randomization will serve as the baseline measurement for efficacy endpoints, while the last measurement prior to first dose of study treatment will serve as the baseline measurement for safety endpoints.

The baseline OCS dose for the primary and secondary variables related to OCS change during the reduction and maintenance periods (Visit 12 and onwards) is defined as the prescribed, daily, average dose prior to randomization (Visit 6) (i.e. the daily dose regimen that a subject is prescribed to be taking up to the time of randomisation, see Section 3.1.2).

For spirometry variables (FEV<sub>1</sub>, FVC and FEF<sub>25-75%</sub>) the measurement recorded at the baseline visit (Visit 6) will be used as baseline. If the Visit 6 measurement is missing, the last non-missing value before Visit 6 will be used as baseline instead. For post-BD measurements, where it is possible to have multiple spirometry records per time point, the first measurement will be used (i.e. the measurement after the first BD administration); for reversibility, this will be the first measurement when the reversibility assessment was considered complete (see Section 3.1.4)

The baseline for ePRO variables (ACQ-6, AQLQ(s)+12, WPAI-CIQ and EQ-5D-5L) will be captured or be derived from what is captured on the ePRO device at Visit 6.

Baseline for the 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 randomisation. If more than 7 daily measures/scores (>50%) within that period are missing, then the baseline will be set to missing.

For analysis of bi-weekly means for Asthma Daily Diary variables where 'at Week 40' is referred to, this should be interpreted as 'at Period 20', as defined in Section 3.3.

For laboratory data, vital signs, physical examination and the dECG measurement, 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 6, this will be assumed to be a pre-dose assessment.

##### **3.1.2 Average Daily OCS Dose**

The OCS dose at baseline and the final dose are defined based on the prescribed dose, expressed as a dose per day, at the time of the relevant visit. If the subject is on a fixed daily dose, then the OCS dose is defined as that prescribed dose. If the subject is on an every other day regimen or any other regimen where a different amount of OCS is to be taken each day, then the OCS dose is defined as the average amount prescribed to be taken each day. For

example, should a subject be on a 10 mg every other day regimen of OCS, their OCS dose will be defined as 5 mg.

### 3.1.3 Absolute and percent change from baseline

Absolute change from baseline outcome variables are computed as

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

Percent change from baseline is computed as

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

If either the post-randomization value or the baseline value is missing, then the absolute or percent change from baseline value will also be set to missing.

### 3.1.4 Reversibility

Reversibility percentage will be computed 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 inhalations, depending on when the reversibility assessment was considered complete.

### 3.1.5 Visit and period windows

For the exacerbation-related analyses no windows will be applied.

For local laboratory data, vital signs, physical examination, dECG and ADA, the visit recorded in the Web Based Data Capture system will be used (i.e. the nominal visit will be presented).

For the central laboratory results, spirometry, AQLQ(S) +12, ACQ-6, and WPAI+CIQ, the variables will be summarized based on the scheduled days with adjusted analysis-defined visit windows as defined in [Table 2](#). EQ-5D-5L will be summarized using the windows as defined in [Appendix A, Table 6](#).

Any data collected at unscheduled visits will be listed, included within the baseline data in shift outputs and will be included in the derivation of maximum /minimum within-period values, 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 (to be defined during the final data review before database lock) of observations for a variable fall outside the adjusted window, sensitivity analysis will be performed where observations are assigned according to the extended windows in Table 2.

**Table 2** Visit windows

Visit	Target Day	Adjusted windows for analyses:	Extended windows for sensitivity analyses:		
			Haematology, AQLQ(S)+12	Post BD Spirometry	Serum chemistry, Urinalysis
Baseline (Week 0) <sup>a</sup>	1	1	1	1	1
Week 2	15	2-21	2-21 <sup>b</sup>	-	-
Week 4	29	22-35	22-42 <sup>b</sup>	-	-
Week 6	43	36-49	-	-	-
Week 8	57	50-63	43-70	-	-
Week 10	71	64-77	-	-	-
Week 12	85	78-91	71-98	2-182	2-154
Week 14	99	92-105	-	-	-
Week 16	113	106-119	99-126	-	-
Week 18	127	120-133	-	-	-
Week 20	141	134-147	127-154	-	-
Week 22	155	148-161	-	-	-
Week 24	169	162-175	155-182	-	-
Week 26	183	176-189	-	-	-
Week 28	197	190-203	183-210	-	-
Week 30	211	204-217	-	-	-
Week 32	225	218-231	211-238	-	155-252
Week 34	239	232-245	-	-	-
Week 36	253	246-259	239-266	-	-
Week 38	267	260-273	-	-	-
Week 40	281	274-294	267-294	183-294	253-308
Week 44 (FU)	309	295-343	295-343	-	-
Week 54 (FU)	379	344-413	344-413	-	-

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

<sup>b</sup> Week 2 is not applicable for AQLQ-12. Week 4 visit window for AQLQ-12 will be 2-42.



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

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

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 or more 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 or more observations are collected on the same day, 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 them, the average of the observations will be used in the analysis.

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

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

### **3.2.1 Primary Efficacy Variable: Percentage change from baseline in prescribed OCS daily dose.**

The primary variable is the percentage change from baseline in the final prescribed, daily, average, OCS dose defined as:

$$\{(\text{Final daily average dose} - \text{baseline daily average dose}) / \text{baseline daily average dose}\} * 100\%$$

Final daily average OCS dose will be derived as follows:

- For any of the cases below, should a subject be placed on a regimen of OCS where different amounts are to be taken each day, their final dose will be defined as the average daily dose, as in Section 3.1.2.

- If a subject's asthma deteriorates during the maintenance phase (weeks 32 to 40), to the point that the subject requires an increase in the daily dose of OCS, that increased dose will be deemed as the subject's final dose for analysis purposes, even if the increased dose is only taken after the 40 week treatment period (otherwise the final dose will be the dose given at Week 38). This does not include an increase due to temporary bolus/bursts of systemic corticosteroids.
- If a subject withdraws from the study or prematurely discontinues IP and does not agree to modified follow-up (i.e. chooses option 2 or 3 in Section 1.2) during the dose reduction phase (Weeks 12 up to 32 – see Appendix, Table 7 for dose titration schedule during the reduction phase), the subject's final dose will be defined as the higher dose level from one step back in the titration schedule. For example, suppose a subject had completed a previous dose reduction period while receiving 10mg daily and was now in a subsequent dose reduction period receiving 5mg daily but withdrew before completing that period. In this case, the subject's final dose level would be defined as 10mg daily. If a subject withdraws as a result of an asthma exacerbation, the OCS dose prior to the systemic steroid burst will be the final dose
- If a subject withdraws from the study or prematurely discontinues IP and does not agree to modified follow-up (i.e. chooses option 2 or 3 in Section 1.2) during the induction phase (Weeks 0 to 12), the subject's final dose will be defined as the dose achieved during dose optimisation.
- If a subject has prematurely discontinued IP, agreed to modified follow-up (option 1 in Section 4.11.2), and the data during follow-up are sufficient to verify the subject's asthma is not worsening, then the subject's final dose will be defined as the last reported dose level. The conditions required to establish that the subject's asthma is not worsening are the same as those required for OCS dose titration (see CSP section 5.1.2) with the exception of investigator judgment.
- If a subject has prematurely discontinued IP, agreed to modified follow-up (option 1) (Section 1.2) and data is not sufficient to verify a subject's asthma is not worsening then the subject's final dose will be defined as the higher dose level from one step back in the titration schedule compared to the last reported dose level when asthma stability could be verified. To verify a subject's asthma is not worsening, they must have data sufficient to verify that they meet all of the following criteria;
  - Pre-BD FEV<sub>1</sub> ≥ 80% of baseline FEV<sub>1</sub> at the final clinic visit.
  - Morning PEF ≥ 80% of baseline mean morning PEF on all 14 days prior to the final visit.
  - Not more than or equal to 50% increase compared to baseline in the percentage of nights with awakenings in the 14 days period prior to the final visit.
  - Mean rescue medication use not more than 4 puffs/day above the baseline mean or 12 puffs/day overall in the 14 days period prior to the final visit.
  - No asthma exacerbation requiring a burst of systemic corticosteroids since the previous visit.

- Only post IP discontinuation data from subjects choosing and remaining on option 1 of the modified follow up will be included in the primary and secondary efficacy analysis. Any data collected will be censored at the time that a subject choose option 2 or 3.

Absolute and percent reduction from baseline in daily OCS dose over time will be tabulated and presented graphically. The OCS dose at each visit will include both prescribed maintenance OCS dose as well as any other OCS medication taken at the time of the visit. This will be repeated for subjects who went through the dose optimization period and for those who had historical optimised dose. This will be repeated for the primary population when it is different than the all-comers population.

### **3.2.2 Secondary Efficacy Variable: Proportion of subjects with a final daily average prescribed OCS dose of $\leq 5.0$ mg**

For each treatment group, the number of subjects with an average final OCS dose  $\leq 5.0$  mg daily will be calculated. The proportion of such subjects will be calculated for each treatment group as:

*Number of subjects with final daily average OCS dose  $\leq 5.0$  mg / number of subjects in treatment group*

Final OCS dose is as described in Section 3.2.1

### **3.2.3 Secondary Efficacy Variable: Proportion of subjects with $\geq 50\%$ reduction from baseline in final daily average prescribed OCS dose**

For each subject, if the calculation in Section 3.2.1 results in a value of -50% or less (more negative), that subject will be classified as having at least a 50% reduction in final daily average OCS dose.

The proportion of such subjects will be calculated for each treatment group as:

*Number of subjects with  $\geq 50\%$  reduction / number of subjects in treatment group.*

### **3.2.4 Secondary Variable: Exacerbation rate**

The annualised asthma exacerbation rate (AAER) up to week 40, in the tralokinumab group will be compared to that seen in the placebo group. The response variable is the number of exacerbations the subject experiences up to Week 40, with the logarithm of the time at risk in years of experiencing an exacerbation included as offset in the model.

An asthma exacerbation is 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 (defined as evaluation and treatment for <24 hours in an ER or UC center) 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

In order to calculate the number of exacerbations experienced by a subject during the 40-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/UC/hospital discharge, whichever occurs later.

Two or more exacerbations with the same start date and end date will be counted as one exacerbation for the purposes of calculating the number and duration of exacerbations for a subject. In the case that one or more exacerbations are recorded as starting or ending during another exacerbation, these will be counted as one exacerbation, using the earliest exacerbation start date and the latest exacerbation stop date to calculate duration.

Additional systemic corticosteroid treatments, ER visits requiring use of systemic corticosteroids, or inpatient hospitalization due to asthma occurring during an exacerbation will not be regarded as a new exacerbation. In order to be counted as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled. If two or more exacerbations are recorded less than 7 days apart, these will be counted as one exacerbation, but the duration period of each exacerbation will be considered separately when calculating exacerbation duration for subject.

Maximum efficacy follow-up time for a subject is approximately 40 weeks; defined as the time from randomization to the date of Visit 26. For a subject lost to follow-up, this will be defined as the time from randomization to the time point after which an exacerbation could not be assessed (i.e. last contact date). Any exacerbations after this time point will not be included in analyses.

Exacerbations that occur after a subject has discontinued IP but before maximum follow-up time will still be accounted for when deriving the total number of exacerbations; and likewise, the follow-up time will reflect the follow-up time regardless of whether or not the subject is still on IP.

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

*Annual Exacerbation Rate = No. of Exacerbations\*365.25 / time at risk of experiencing an exacerbation.*

### **3.2.5 Exploratory Variable: Area under the prescribed daily average OCS dose curve**

Area under the OCS dose curve will be calculated using the time period from baseline to Week 40. The dose at each visit includes both maintenance OCS dose and any other OCS taken in a temporary burst at the time of the visit. If a subject withdraws from the study, the final dose as defined in Section 3.2.1 will be used for the time from withdrawal to Week 40. The area under the curve (AUC) will be calculated using the trapezoidal method for the time interval between each visit.

The AUC will be determined for each time interval, with the segment area computed as per example (e.g. interval between times a and b with respective dose values  $h_1$  and  $h_2$ ):

$$AUC_1 = \frac{b - a}{2} \times (h_1 + h_2)$$

then sum  $AUC_1$  to  $AUC_{\text{last time period}}$  for the 40 week treatment period.

### **3.2.6 Exploratory Variable: Proportion of subjects in different categories of reduction from baseline in final daily average prescribed OCS dose**

For each subject, the calculated reduction in Section 3.2.1 will be categorised into:

Increase,

No change,

>0- <50% reduction,

≥50- <75% reduction,

≥75- <90% reduction

≥90- <100% reduction

100% reduction

The proportion of such subjects will be calculated for each treatment group as:

*Number of subjects in each category/number of subjects in treatment group*

**3.2.7 Exploratory Variable: Proportion of subjects with  $\geq 25\%$  reduction from baseline and with final daily average prescribed OCS dose  $\leq 5.0$  mg daily**

For an individual subject, if the calculation in Section 3.2.1 results in a reduction of 25% or greater and if the average final OCS dose  $\leq 5.0$  mg daily, that subject will be classified accordingly.

The proportion of such subjects will be calculated for each treatment group as:

*Number of subjects with  $\geq 25\%$  reduction from baseline and final daily average OCS dose  $\leq 5.0$  mg daily / number of subjects in treatment group.*

Final dose is as defined in Section 3.2.1.

**3.2.8 Exploratory Variable: Proportion of subjects with  $\leq 5.0$  mg reduction from baseline in daily average prescribed OCS dose**

For each treatment group, the number of subjects with change from baseline to final visit in average daily OCS dose  $\leq 5.0$  mg will be calculated. The proportion of such subjects will be calculated for each treatment group as:

*Number of subjects with  $\leq 5.0$  mg reduction from baseline in daily average OCS dose at final visit / number of subjects in treatment group.*

Final dose is as defined in Section 3.2.1.

**3.2.9 Supportive variable: Time to first exacerbation**

Time (in days) from randomization to the first asthma exacerbation will be used as a supportive variable to the secondary variable in Section 3.2.4 and is calculated as follows:

*Start Date of first asthma exacerbation – Date of Randomization + 1.*

The time to first asthma exacerbation for subjects who do not experience an asthma exacerbation during the treatment period will be censored at the date of their last visit for the 40 week treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up subjects).

**3.2.10 Supportive variable: Proportion of subjects with  $\geq 1$  asthma exacerbation during 40 week treatment period**

The proportion of subjects with  $\geq 1$  asthma exacerbation during the 40 weeks of treatment will be a supportive variable to the secondary variable in Section 3.2.4. The outcome variable will categorize each subject as having at least one asthma exacerbation or not (yes=1/no=0).

The proportion of such subjects will be calculated for each treatment group as:

*Number of subjects with  $\geq 1$  asthma exacerbation during the 40 week treatment period/  
number of subjects in treatment group*

### **3.2.11 Supportive variable: Annual rate of asthma exacerbations that are associated with an ER or UC visit or a hospitalization**

The AAER that are associated with an ER or UC visit or a hospitalization (defined in Section 3.2.4) will be a supportive variable to the secondary variable in Section 3.2.4.

The number of asthma exacerbations that are associated with an ER or UC visit or a hospitalization experienced by a subject during the 40-week treatment period will be derived according to the same rule for start and end in Section 3.2.4.

Maximum follow-up time is approximately 40 weeks, and the follow-up time is derived as described in Section 3.2.4.

Additionally, for the production of descriptive statistics, the annual rate of asthma-related ER or UC visits and hospitalizations will be calculated using the same methodology as the annualized rate of exacerbations described in Section 3.2.4.

### **3.2.12 Exploratory variables: Percentage change from baseline in lung function variables**

Percentage and absolute change from baseline in tralokinumab group will be compared to that in the placebo group at Week 12 and Week 40 for FEV<sub>1</sub>, FVC and FEF<sub>25-75%</sub>.

These variables will be calculated as described in Section 3.1.3 and on the pre-BD and the post-BD measurements. 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 5.1.4 of the CSP contains further details of the spirometry recordings.

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

Patient-reported outcomes (PRO) data will be captured via an ePRO device. The definition of secondary outcome variables based on the ePRO are provided in the following sections. For all outcomes based on the ePRO devices, analyses will be based on data up to and including week 40.

For asthma symptom score, rescue medication use and home peak expiratory flow, 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 divided by the number of non-missing daily measures/scores. 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’. Note that the first bi-weekly mean in the treatment period will be based on the evening recording on day 1 up to and including the morning recording on day 15. The daytime score is recorded in the evening and the night-time score is recorded the following morning.

Bi-weekly periods are defined as follows (where Day 1 is the day of randomization)

Bi-weekly Period	Label
Baseline: as defined in Section 3.1.1	(Day -14 to 1) Baseline
Period 1: Evening of Day 1 – Morning of Day 15	Day 1 – 15 (Week 2)
Period 2: Evening of Day 15 – Morning of Day 29	Day 15 – 29 (Week 4)
Period 3: Evening of Day 29 – Morning of Day 43	Day 29 – 43 (Week 6)
Period 4: Evening of Day 43 – Morning of Day 57	Day 43 – 57 (Week 8)
Period 5: Evening of Day 57 – Morning of Day 71	Day 57 – 71 (Week 10)
Period 6: Evening of Day 71 – Morning of Day 85	Day 71 – 85 (Week 12)
Period 7: Evening of Day 85 – Morning of Day 99	Day 85 – 99 (Week 14)
Period 8: Evening of Day 99 – Morning of Day 113	Day 99 – 113 (Week 16)
Period 9: Evening of Day 113 – Morning of Day 127	Day 113 – 127 (Week 18)
Period 10: Evening of Day 127 – Morning of Day 141	Day 127 – 141 (Week 20)
Period 11: Evening of Day 141 – Morning of Day 155	Day 141 – 155 (Week 22)
Period 12: Evening of Day 155 – Morning of Day 169	Day 155 – 169 (Week 24)
Period 13: Evening of Day 169 – Morning of Day 183	Day 169 – 183 (Week 26)
Period 14: Evening of Day 183 – Morning of Day 197	Day 183 – 197 (Week 28)
Period 15: Evening of Day 197 – Morning of Day 211	Day 197 – 211 (Week 30)
Period 16: Evening of Day 211 – Morning of Day 225	Day 211 – 225 (Week 32)
Period 17: Evening of Day 225 – Morning of Day 239	Day 225 – 239 (Week 34)
Period 18: Evening of Day 239 – Morning of Day 253	Day 239 – 253 (Week 36)
Period 19: Evening of Day 253 – Morning of Day 267	Day 253 – 267 (Week 38)
Period 20: Evening of Day 267 – Morning of Day 281	Day 267 – 281 (Week 40)

Where a total score is calculated within a day (e.g. Asthma symptom score), this calculation will span two calendar days - the daytime value recorded in evening of day X, and the night-time value recorded on morning of day x+1. E.g. the Asthma Symptom score on Day 1 will be the day time score recorded on the evening of Day 1 + the night-time score recorded on the morning of Day 2.

Where only night-time scores/results are of interest, the morning entries on the second day of a period up to and including the morning entry on the last day of the period (or morning of the last day of study for the last period/last IP intake) will be considered.



Where only daytime scores/results are of interest, the evening entries on the first day of the period up to and including the evening entry on the second last day of the period (or evening before the last day of study/last IP intake) will be considered.

Change from baseline will be calculated as described Section 3.1.2

### **3.3.1 Exploratory Variable: Asthma symptom score**

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

The daily asthma symptom total score will be calculated by taking the sum of the night-time and daytime asthma symptom scores recorded each 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 change from baseline in bi-weekly mean daily asthma total symptom score. Bi-weekly means and change from baseline for daytime and night-time scores will also be calculated.

### **3.3.2 Exploratory Variable: Rescue medication use**

The number of rescue medication inhalations and nebulizer treatments taken will be recorded by the subject in the Asthma Daily Diary twice daily. Daytime use is recorded in the evening and night-time use is recorded the following 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 ePRO 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 change from baseline in the number of inhalations (puffs) per day will be calculated as the outcome variable.

### **3.3.3 Exploratory Variable: Home peak expiratory flow (morning and evening)**

Bi-weekly mean absolute changes from baseline in morning and evening PEF will be calculated.

### **3.3.4 Exploratory Variable: Nights with awakening due to asthma**

Bi-weekly mean change from baseline in the number (percentage) of nights with awakening due to asthma that required rescue medication will be calculated as the outcome variable.

### **3.3.5 Exploratory Variable: 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. Subjects will be asked to complete ACQ-6 once every 2 weeks. 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 baseline will be the unweighted mean of the 6 questions at Visit 6.

The outcome variable for the ACQ-6 will be the change in mean score from baseline at Week 12 and Week 40. The change from baseline for each questions will also be calculated.

Other variables based on ACQ-6 that will be reported are:

- ACQ-6-responder (Yes=1/No=0) at each post-randomization assessment during the treatment period:
  - 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) at each post-randomization assessment during the treatment period:
  - Improvement: Change from baseline ACQ-6 score  $\leq -0.5$

- No change:  $-0.5 < \text{Change from baseline ACQ-6 score} < 0.5$
- Deterioration:  $\text{Change from baseline ACQ-6 score} \geq 0.5$
- Subjects asthma control as measured by ACQ-6 score at each post-randomization assessment during the treatment period:
  - Well controlled :  $\text{ACQ-6 score} \leq 0.75$
  - Partly controlled :  $0.75 < \text{ACQ-6 score} < 1.5$
  - Not well controlled :  $\text{ACQ-6 score} \geq 1.5$

### 3.3.6 Exploratory Variable: Asthma quality of life questionnaire for 12 years and older (AQLQ(S) +12)

In the AQLQ(S) +12 the subjects are asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). Subjects will be asked to complete AQLQ(S) +12 once every 4 weeks.

The overall score is calculated as the mean of the responses to all questions. The 4 individual domain scores (4 domains assessing 1) symptoms, 2) activity limitations, 3) emotional function, and 4) environmental stimuli) are the means of the responses to the questions in each of the domains. The question numbers on the AQLQ(S)+12 questionnaire relating to each domain are presented in [Table 3](#).

**Table 3 AQLQ(S) +12 Domains**

Domain	AQLQ(S)+12 question numbers
Symptoms	6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitations	1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function	7, 13, 15, 21, 27
Environmental Stimuli	9, 17, 23, 26

If response to any of the questions is missing the overall score will be missing, if response to a question within a domain is missing, the score for that domain will be missing.

The outcome variable for the AQLQ(S) +12 will be the change in overall score from baseline at Week 12 and Week 40. Change from baseline in each of the 4 domains will also be calculated.

Other variables based on AQLQ(S) +12 to be reported include:

- AQLQ(S) +12 -responder (Yes=1/No=0) at each post-randomization assessment during the treatment period:
  - Responder: Change from baseline AQLQ(S) +12 score  $\geq 0.5$
  - Non-responder : Change from baseline AQLQ(S) +12 score  $< 0.5$
- AQLQ(S) +12 -response (Improved/No Change / Deterioration) at each post-randomization assessment during the treatment period:
  - Improvement: Change from baseline AQLQ(S) +12 score  $\geq 0.5$
  - No change:  $-0.5 < \text{Change from baseline AQLQ(S) +12 score} < 0.5$
  - Deterioration: Change from baseline AQLQ(S) +12 score  $\leq -0.5$

### **3.3.7 Exploratory Variable: European quality of life-5 dimensions-5 levels (EQ-5D-5L)**

The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty.

The subject will be asked to indicate his/her current health state weekly by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a VAS, where the subject will be asked to rate current health status on a scale of 0-100, with 0 being the worst imaginable health state.

The change from baseline in VAS will be calculated at each visit.

### **3.3.8 Exploratory Variable: Health care resource utilization**

Health care resource utilization due to asthma will be collected by the Investigator/authorized delegate at each visit as specified in the protocol and recorded in the HEVENT module in the electronic case report form (eCRF).

Study period number of days/times will be calculated for each subject for the following variables:

- Ambulance transport
- Hospitalization (number of visits and days in hospital)
  - Intensive care (days in intensive care)
  - General care (days in general care)

- ER visit
- Visit to specialist
- Visit to primary health care physician
- Other health care visit
- Home visit, physician
- Home visit, other health care
- Telephone call, physician
- Telephone call, nurse

The study period number per subject will be determined as:

*Study period number = Sum of 'total No. of times/days' as entered in HEVENT up to Week 40.*

### **3.3.9 Exploratory Variable: The Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ)**

The WPAI+CIQ questionnaire is a 10-item questionnaire that assesses productivity and activity impairment over the previous week. Subjects will be asked to complete WPAI+CIQ once every 2 weeks.

There are a maximum of 10 questions and a minimum of 3 questions that will be completed by subjects as follows

1. Currently employed (yes/no)
2. Hours missed work due to health problems
3. Hours missed work due to other reasons
4. Hours actually worked
5. Degree health affected productivity while working (0-10 scale, with 0 meaning no effect)
6. Attends class in an academic setting (yes/no)
7. Hours missed class due to health problems
8. Hours actually attended class
9. Degree health affected productivity while attending class (0-10 scale, with 0 meaning no effect)
10. Degree health affected regular activities (other than work or class) (0-10 scale, with 0 meaning no effect)

If the answer to question 1 is 'No, not currently employed', then the subject should skip to question 6. If the answer to question 6 is 'No, not currently attending class', then the subject should skip to question 10.

The WPAI+CIQ provide 4 scores:

- Absenteeism (work or class time missed),
- Presenteeism (impairment at work or class/reduced on-the-job effectiveness),
- Work productivity loss (overall work or class impairment/absenteeism plus presenteeism)
- Activity impairment.

WPAI+CIQ outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

For each time point at which the WPAI-CIQ is administered, the following descriptive statistics (if applicable) (n, total number of hours, mean per subject, standard deviation (SD), median, minimum and maximum) will be reported for those who are employed:

- # employed
- % of all subjects employed
- # of work hours missed due to asthma
- Absenteeism due to asthma
- Presenteeism due to asthma
- Work Productivity Loss
- Activity impairment

The following formulas will be used to calculate each of the outcome measures listed above:

- # currently employed – Yes in response to Question 1
- # of work hours missed due to asthma – as responded in Question 2
- Absenteeism =  $Q2/(Q2+Q4)$
- Presenteeism =  $Q5/10$
- Work Productivity Loss =  $Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)]$

- Activity Impairment =  $Q10/10$

Similarly, the following will be reported for those subjects who are in school:

- # in school
- % of all subjects in school
- # of class hours missed due to asthma
- Absenteeism due to asthma
- Presenteeism due to asthma
- Class Productivity Loss
- Activity impairment

The following formulas will be used to calculate each of the outcomes measures listed above:

- # in school - Yes to Question 6
- # of class hours missed due to asthma – as responded on Question 7
- Absenteeism due to asthma -  $Q7/(Q7+Q8)$
- Presenteeism due to asthma –  $Q9/10$
- Class Productivity Loss –  $Q7/(Q7+Q8) + [(1-Q7/(Q7+Q8))x(Q9/10)]$
- Activity Impairment =  $Q10/10$

In addition, activity impairment will be presented for those who are not employed, not in school, and all subjects.

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

The following safety data will be collected: reported Adverse Events (AEs), haematology, clinical chemistry, urinalysis, physical examination (complete and brief), 12-lead dECG, vital signs, and medical history.

Change from baseline (as defined in Section 3.1.1) to each scheduled post-baseline time point will be calculated for relevant measurements.

### **3.4.1 Adverse events**

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

AE data will be categorized according to their onset date into the following periods:

- AEs occurring during run-in/optimization (onset date  $\geq$  Visit 1 and before the first dose of IP)
- AEs occurring during study (onset date  $\geq$  the first day of IP and  $\leq$  Visit 28 (Week 54))
- AEs occurring during treatment (onset date  $\geq$  the date of first dose of IP and  $\leq$  the date of last dose of IP + 2 weeks)
- AEs occurring post-treatment (onset date  $>$  the date of last dose of IP + 2 weeks and  $\leq$  Visit 28 (Week 54))

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 as occurring during treatment. 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 as occurring during treatment. 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 review all AEs and identify those that merit special attention. These AEs fall into three categories:

- AEs possibly related to administration of biologics (eg, anaphylaxis/hypersensitivity reactions and injection site reactions)
- AEs possibly related to the mechanism of action of tralokinumab as an IL-13 blocking agent (eg, infections such as severe, viral, invasive fungal, and parasitic, malignancy, cardiovascular/cerebrovascular events, pregnancy/spontaneous abortion and increased eosinophils)
- AEs reported for other biologics in this class (eg, 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 5, Table 6, Table 7 and Table 8 in Section 5.1.6.1 of the CSP, will be collected. Laboratory data will be reported in SI units.

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 of these reference ranges will be flagged.

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

For the purposes of haematology, clinical chemistry and urinalysis shift tables, baseline will be defined as the latest non-missing assessment prior to first dose and during 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), Gamma-Glutamyl Transpeptidase (GGT) and total bilirubin (TBL), the multiple of the AstraZeneca upper limit of the normal (ULN) range will be calculated for each data point.

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

ie, 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:

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

### 3.4.4 dECGs

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

The outcome of the overall evaluation is to be recorded as normal/abnormal in the 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 Visit 1 complete physical examination will be recorded as normal or abnormal. Each component of the complete physical examinations (from Visit 6 onwards) will be recorded as normal, same as Visit 1, or new/aggravated.

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

### 3.4.6 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 of the CSP.

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

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 of these reference ranges/delta limits will be flagged.

**Table 4 Vital signs reference ranges**

Parameter	Standard Units	Lower Limit	Upper Limit	Change Criteria
Diastolic Blood Pressure (sitting)	mmHg	<60	>100	±15
Systolic Blood Pressure (sitting)	mmHg	<90	>160	±30
Pulse (sitting)	Beats/min	<50	>100	±20
Respiratory Rate	Breaths/Min	<8	>20	
Body Temperature	Celsius	<36	>37.5	
Weight	kg	<40	>150	

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

$$BMI = kg/m^2$$

This calculation is performed on the eCRF and this will be the value that is reported.

### 3.4.7 Medical History

The principle for imputing incomplete diagnosis dates when calculating the number of years since diagnosis (earliest possible date) is shown in [Table 5](#) below:

**Table 5 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 Visit 6(Week 0),, at multiple time points before IP administrations (trough sampling) during the treatment period, and at selected timepoints in the follow-up period of the study. 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 4.2.6.18](#).

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

Tralokinumab serum concentrations will be tabulated by time 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, evaluation of ADA impact on the PK, PD, efficacy and safety will be summarized in the CSR. Summaries of tralokinumab serum concentrations by time will be summarized by ADA status (positive vs negative) for the tralokinumab treatment group.

## **3.6 Calculation or derivation of other variable(s)**

### **3.6.1 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 the dosing frequency time:

$$\text{Extent of exposure (days)} = (\text{Last dosing date} + 2 \text{ weeks}) - \text{First dosing date} + 1.$$

In addition the total number of dosing occasions will be calculated per subject.

Compliance is defined as:

$$\text{Compliance (\%)} = (\text{Total number of dosing occasions} / \text{total number of dosing occasions expected}) \times 100$$

The total number of dosing occasions expected is calculated based on a planned dose, every 2 weeks, up until the time a subject discontinues IP.

## **4. ANALYSIS METHODS**

### **4.1 General principles**

The analysis of the study efficacy endpoints will include all data captured during the 40 week treatment period. This includes data regardless of whether IP was prematurely discontinued or delayed (depending on the subjects option once they discontinue IP), and/or irrespective of protocol adherence, unless the subject withdraws consent or assent to study participation.

Due to the uncertainty of the quality/usability of data that will be collected for subjects initially or ultimately choosing follow-up options 2 or 3 (as defined in Section 1.2), efficacy analysis summaries will include only data from subjects who choose option 1, up to the point they complete the study to 40 weeks, withdraw from the study, or migrate to a different option. For reporting of safety data, with the exception of AE and concomitant medication presentations, only data from subjects who choose option 1, up to the point they withdraw from the study or migrate to a different option will be included.

If a subject is entered into the incorrect randomization stratum category, they will be analyzed accorded to their randomized stratum. A summary table which counts any subjects that have been misclassified 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, SD, median, and range. All tables will be produced for scheduled visits only, other than where specified in Section 3.1.5. All data will be listed. Data listings will be sorted by treatment and subject number.

Minimum and maximum values will be reported to the same degree of precision as the raw data unless otherwise stated. Mean, median, SD and confidence intervals (CIs) will be reported to one further degree of precision. Percentage values will rounded and presented to one decimal place. If the calculated percentage is  $> 0.0\%$  but  $< 0.1\%$  then  $< 0.1\%$  is to be presented in the relevant table and/or listing. If the calculated percentage is 100%, this will be reported with no decimal places.

All hypothesis testing will be reported using 2-sided tests. P-values will be rounded to 3 decimal places. P-Values below 0.0005 will be denoted as  $< 0.001$ .

#### **4.1.1 Primary Population for primary and secondary objectives**

The primary population for statistical testing will be determined by the distribution of the biomarker FeNO at baseline and the prevalences of subjects within the FeNO High ( $\text{FeNO} \geq 37$  ppb) and FeNO Mid ( $25 \leq \text{FeNO} < 37$  ppb) subgroups. As defined in Section 3.1.1, the baseline biomarker value is the last value prior to randomization (Visit 6). The distribution of FeNO in TROPOS is unknown. If the prevalence of the FeNO High subgroup is at least 50%, that subgroup will be used as the primary population for statistical testing. Otherwise, if the combined prevalence of the FeNO High and FeNO Mid subgroups is at least 50%, the combined FeNO Mid/High subgroup will be used as the primary population. Otherwise, the all-comers population will be used as the primary population.

Results of the primary and secondary efficacy objectives and presentation of Demographics and select Safety will be presented for the full study population, subgroups based on  $\text{FeNO} \geq 37$  ppb and  $< 37$  ppb, as well as the subgroups based on  $\text{FeNO} \geq 30$  ppb and  $< 30$  ppb when FeNO Mid+High is the primary population. The statistical testing in Section 4.1.2 will begin with the primary population and potentially include the all-comer population. Analyses of other domains (i.e. Safety, Exposure, etc.) will be done only for the full study population unless otherwise noted.

Because only one set of statistical tests will be carried out, and the type I error within each possibility is 5%, the overall type I error for the study remains at 5% assuming a global null hypothesis of no treatment effect within any of the FeNO subgroups.

#### **4.1.2 Testing strategy for primary and secondary objectives**

To account for multiplicity when testing the primary and secondary endpoints, a hierarchical testing strategy will be used for primary and secondary outcomes in the selected primary population:

If the primary population is defined as a biomarker positive population (column A in Figure 2) AND treatment effect is shown in all four endpoints in the primary population, then the all-comer population will be tested in the same sequential order. If the primary population is defined as the all-comer population (column B in Figure 2), then the hierarchical testing will not include any tests of any biomarker positive population.

No adjustments will be made for tests of safety or exploratory efficacy variables. Although p-values will be calculated for the above-mentioned endpoints, any results reported for these variables will be considered nominal (i.e., unadjusted) and will be interpreted in an exploratory way.

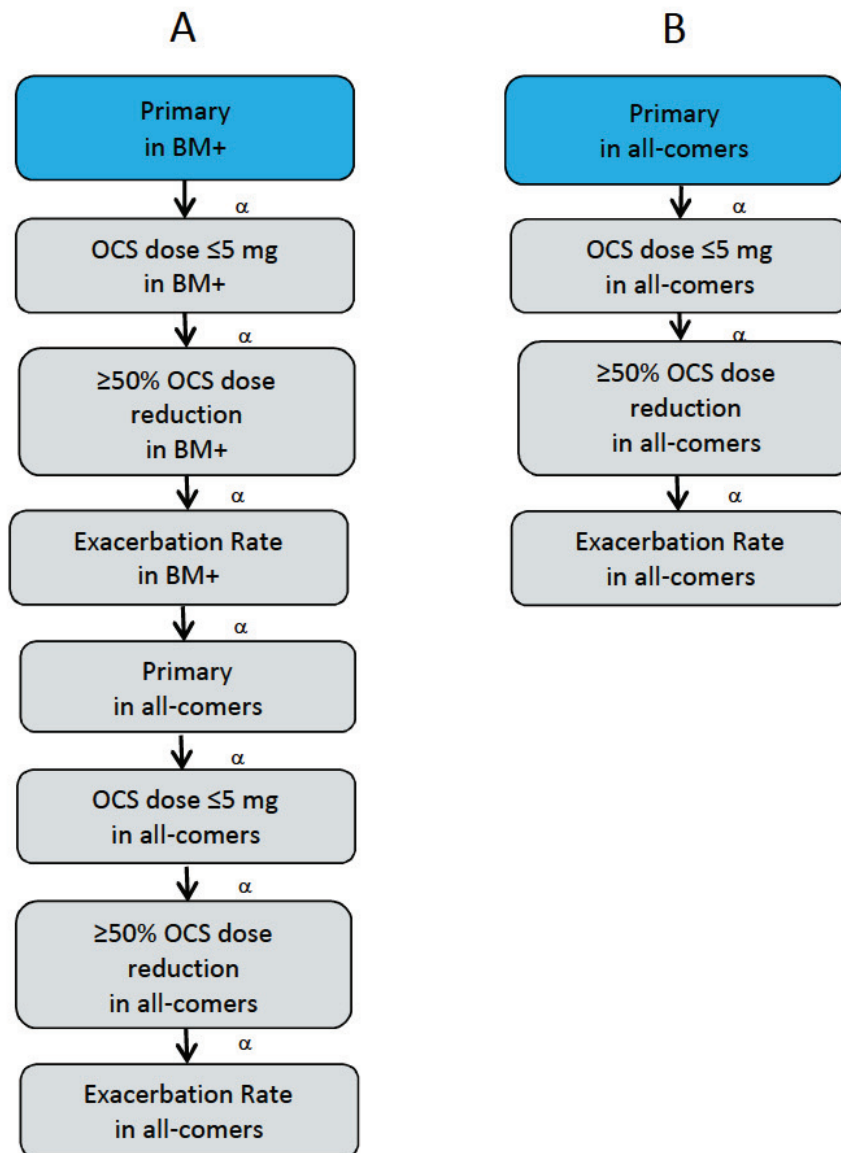
The difference in the proportion of subjects with final daily average OCS dose  $\leq 5.0$  mg will only be tested if the p-value for the test of difference in percentage change in final daily average OCS dose is less than 0.05.

The difference in the proportion of subjects with  $\geq 50\%$  reduction in final daily average OCS dose will only be tested if both p-values for the tests of difference in percentage change in final daily average OCS dose and difference in the proportion of subjects with final daily average OCS dose  $\leq 5.0$  mg are less than 0.05.

The reduction in AAER will only be tested if all p-values for the tests of differences in percentage reduction in OCS, difference in proportion of subjects with final OCS dose  $\leq 5.0$  mg, and difference in proportion of subjects with  $\geq 50\%$  reduction in OCS dose are less than 0.05.

This testing strategy is considered to provide strong control of the FWER in this situation given that the prevalence of baseline FeNO in TROPOS is unknown and that it is pharmacologically plausible that the placebo-controlled efficacy isn't negative in any biomarker subpopulations.

**Figure 2 Testing Strategy**



## 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 (subjects who completed IP and study, and subjects who discontinued IP but completed study assessments), 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 option of follow up (Section 1.2) and will also be listed.

Kaplan-Meier plots will be produced summarizing the time (in days) to discontinuation of IP and withdrawal from the study.

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

Various baseline characteristics will also be summarized by treatment and listed for the FAS. These include medical, surgical and respiratory disease histories, weight, height and BMI, smoking status, history of allergy, OCS dose at baseline, FEV<sub>1</sub> (pre and post-BD) and FEV<sub>1</sub> reversibility at baseline, asthma duration, age at onset of asthma, asthma medications, the number of asthma exacerbations in the previous 12 months, the number of asthma exacerbations requiring hospitalizations in the previous 12 months, phadiatop allergy test results, AQLQ(S)-12, and ACQ-6. Data collected at the latest pre-randomisation assessment will be summarised.

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

#### **4.2.2 Prior and Concomitant Medications**

The number and percentage of subjects receiving each medication (by 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: medication start date is before 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 categorised as ‘Concomitant’ 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.

The concomitant during treatment table will be further split to summarize Asthma medications separately for that period. Asthma medications will be identified using the ‘reason for therapy’ collected on the eCRF. Where 'Disease under study' is chosen, medications will be included.



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 and OCS medications. The number of subjects using maintenance asthma medications at baseline will also be summarised. In addition, the total number of days of systemic corticosteroid treatment associated with asthma exacerbations per patient from the first day of IP up to Week 40 will also be summarised.

Concomitant medications on treatment will be presented for allowed and disallowed medications separately. Disallowed medications will include medications defined as prohibited according to Appendix H of the CSP). They will be defined following 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 (AZDD). 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, regardless of level of follow up chosen will, where possible and relevant, be included in post-treatment medication summaries.

#### **4.2.3 Exposure and compliance**

Extent of exposure to IP, total number of dosing occasions, total number of injections and compliance to study treatment will be summarized by treatment group and listed, 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**

The primary efficacy variable is the percentage change from baseline to Week 40 in the subject's final daily, average, prescribed, OCS dose.

The null hypothesis is that the average percentage change in OCS dose on tralokinumab is equal to the average percentage change in OCS dose on placebo. The alternative hypothesis is that the average percentage change in OCS dose on tralokinumab is not equal to the average percentage change in OCS dose on placebo, ie:

*H<sub>0</sub>: difference in average % change of OCS dose (tralokinumab vs. Placebo)=0*

*H<sub>a</sub>: difference in average % change of OCS dose (tralokinumab vs. Placebo)≠0*

The average percentage change in OCS dose in tralokinumab treatment group will be compared to the average percentage change in OCS dose in the placebo group using an analysis of covariance (ANCOVA) model utilizing a sandwich estimator for the variance.

The response variable in the model is the percentage change in OCS dose from baseline to Week 40, Visit 26. If the Week 40 dose is not available, the final dose will be used and derived as per Section 3.2.1. The model will include treatment group as a fixed effect and baseline OCS dose as a continuous covariate. Analysis of the primary endpoint will be repeated for FeNO High with an analysis that will include all data and the model will also include a main effect for membership in the FeNO High and an interaction term for the interaction between treatment and FeNO High. If FeNO Mid+High is the primary population, this analysis will be repeated with an analysis that includes all data and a model that includes a main effect for membership in FeNO Mid+High and an interaction term for the interaction between treatment and FeNO Mid+High. The OM option will be used to adjust the coefficients for the LSMEANS to reflect the observed data. All group comparisons from ANCOVA model will be based on Type III sums of squares. Least Square (LS) mean and SE will be presented for each treatment group (within each FeNO subgroup as applicable) as well as the LS mean for the comparison of tralokinumab versus placebo (tralokinumab - placebo), corresponding 95% confidence interval (CI), will be presented.

LS means and 95% CIs for each treatment group will also be presented graphically at each post baseline visit. OCS dose and percentage change from baseline will also be listed.

In order to illustrate the ability to identify the optimized baseline OCS dose, a table comparing the OCS dose at study entry to the optimized baseline OCS dose will be presented. Subjects with historical optimization of OCS dose will be included and also indicated in parentheses.

A cumulative distribution plot of the percent reduction in OCS dose from baseline will be presented that shows, for each treatment group, for each observed percent reduction the proportion of subjects in that treatment group who achieved that level of reduction or greater (more reduction). For this plot, all subjects with increase from baseline will be presented as having 0% reduction.

The assumptions of the parametric ANCOVA model will be checked (using blinded data, at the final data review meeting) by visual inspection of the residuals. In case the underlying assumptions are clearly not met, an alternative, suitable, non-parametric analysis will be considered.

A p-value for the comparison of the primary endpoint using a Wilcoxon rank-sum test will be presented. This p-value will be included as a reference and will not be included in the hierarchical testing strategy.

#### **4.2.4.1 Subgroup analyses**

The consistency of treatment effect on the primary endpoint across different subgroups will be explored. For each subgroup separately, a subgroup (if not already included) and a subgroup-by-treatment term will be added to the ANCOVA model used in the primary analysis. The estimates (and 95% CIs) for the interaction effects, and estimates (and 95% CI) of treatment

differences within each subgroup level will be reported. Any subjects with a missing value for the defined subgroup will be excluded from the analysis of that subgroup.

The subgroups to be explored will include:

- ICS dose at randomization (medium , high) – Note: the process of categorizing ICS dose into these subgroups is detailed in a separate document (ICS Final v1.0)
- OCS dose at randomization: ( $\leq 10$  mg versus  $> 10$  mg prednisone or prednisolone)
- FeNO baseline group: above ( $\geq$ ) and below ( $<$ ) 37 ppb. See Below
- Geographical region (North America [*incl. US*], Western Europe [*incl. Belgium, Germany, Netherlands and France*], Eastern Europe [*incl. Poland and Ukraine*])
- Country
- Race (as entered in the eCRF)
- Gender (Male, Female)
- BMI (above ( $>$ ) and below ( $\leq$ ) 30 kg/m<sup>2</sup>) – to be produced for adults only.
- Exacerbations in previous 12 months (above ( $>$ ) and below ( $\leq$ ) 2)

These analyses are exploratory and the results from these analyses will not affect the choice of terms used in the model for the primary analysis. The performance of each subgroup analysis will be conditional on a minimum number of subjects being present in each subgroup. This minimum will be specified during the final blind data review, before database lock.

The FeNO baseline group will only be presented as a subgroup analysis where the FeNO High subgroup is NOT selected as the primary population.

When the primary population is different from the all-comers population, the subgroup analysis above will be repeated within both the primary population and the all-comers population.

#### **4.2.5 Analysis of secondary variable(s)**

All secondary variables will be analyzed based on the FAS as well as the FeNO High subgroup (FeNO  $\geq 37$  ppb). Analyses of the secondary variables will be repeated within subgroups based on FeNO  $\geq 30$  ppb and FeNO  $< 30$  ppb when the FeNO Mid+High is the primary population. Similar to the primary analysis, the secondary analysis for biomarker subgroups will be implemented by including all subjects and extending the respective models

with an effect for membership in the appropriate FeNO subgroup and an interaction between treatment group and FeNO subgroup.

#### **4.2.5.1 Proportion of subjects with a final daily average prescribed dose of $\leq 5.0$ mg.**

The proportion in the tralokinumab group will be compared with the proportion in the placebo group using a logistic regression. The model will include treatment group as a fixed effect and baseline OCS dose as a continuous covariate.

An odds ratio will be presented together with associated 95% CI and 2-sided p-value for tralokinumab versus placebo. The number and percentage of subjects reaching  $\leq 5.0$ mg will also be summarized by randomized treatment for both populations.

#### **4.2.5.2 Proportion of subjects with $\geq 50\%$ reduction from baseline in the final daily average prescribed OCS dose**

The proportion in the tralokinumab group will be compared with the proportion in the placebo will be summarized and analyzed using the approach as described in Section [4.2.5.1](#)

#### **4.2.5.3 Exacerbation rate**

The AAER in the tralokinumab group will be compared to that seen in the placebo group using a negative binomial model. The response variable in the model will be the number of asthma exacerbations experienced by a subject, over the 40 week treatment period. The model will include covariates of treatment group (tralokinumab Q2W and placebo), OCS dose at baseline and number of exacerbations in the year before the study. The OM option will be used for the LSMEANS estimates. The logarithm of the subject's corresponding follow-up time in years will be used as an offset variable in the model to adjust for subjects having different exposure times during which the events occur.

The offset variable will be the logarithm of the time at risk in years of experiencing an exacerbation: [follow-up time (follow-up date – date of randomisation + 1) minus the number of days the subject experiences a protocol defined exacerbation including the subsequent 7 days (when a further exacerbation would not be considered as a second exacerbation)]/365.25.

The standard parameterization approach (NB2) of the Negative Binomial model will be applied ( [Hilbe 2011](#)) using PROC GENMOD (SAS procedure).

The estimated treatment effect (ie, the rate ratio of tralokinumab versus placebo), corresponding 95% confidence interval (CI), and p-value for the rate ratio will be presented. In addition, the AAER and the corresponding 95% CI within each treatment group will be presented.

The estimated treatment effect (ie, the rate ratio of tralokinumab versus placebo) and corresponding 95% CI will also be presented on a forest plot and exacerbation information will be listed.

Only exacerbations that can be determined to be protocol defined exacerbations (CSP Section 5.1.1) will be included the analyses and 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 Section 3.2.4 being fulfilled. From the EXACA form on the eCRF, for a given exacerbation this will include exacerbations where EXACDRY= 'Yes' and at least one of the following a) EXSCORT = 'Yes' b) EXSCORT = 'Yes' and EXERTRT = 'Yes' c) HOSPIT = 'Yes'.

#### **4.2.6 Analysis of exploratory/supportive variables**

##### **4.2.6.1 Area under the prescribed daily average OCS dose curve**

The area under the daily average OCS dose curve will be addressed as a supportive variable to the primary objective will be summarized and analyzed using the ANCOVA approach defined for the primary variable, as described in Section 4.2.4

##### **4.2.6.2 Proportion of subjects in different categories of reduction from baseline in final daily average prescribed OCS dose**

The proportion of subjects in different categories of reduction from baseline in final daily average OCS dose will be addressed as a supportive variable to the primary objective. The proportion of subjects with an increase, no change, >0- <50%,  $\geq 50$  -<75%,  $\geq 75$  -<90%  $\geq 90$  -<100% 100% reduction (no OCS) in final daily average OCS dose in the tralokinumab group will be compared with the proportion in the placebo group controlling for baseline OCS dose.

A proportional odds ratio will be presented together with associated 95% CI and 2-sided p-value.

##### **4.2.6.3 Proportion of subjects with $\geq 25\%$ reduction from baseline and with final daily average prescribed OCS dose $\leq 5.0$ mg daily**

Proportion of subjects with  $\geq 25\%$  reduction from baseline and with final daily average prescribed OCS dose  $\leq 5.0$  mg daily will be addressed as a supportive variable to the secondary objectives and will be summarized and analyzed using the approach defined for the proportion of subjects with final daily average prescribed OCS dose  $\leq 5.0$  mg daily, as described in Section 4.2.5.1.

##### **4.2.6.4 Proportion of subjects with $\leq 5.0$ mg reduction in final daily average prescribed OCS dose**

The proportion of subjects with  $\leq 5.0$  mg reduction from baseline in final daily average prescribed OCS dose will be addressed as a supportive variable to the secondary objectives and will be summarized and analyzed using the approach defined for the proportion of

subjects with final daily average prescribed OCS dose  $\leq 5.0$  mg daily, as described in Section 4.2.5.1.

#### 4.2.6.5 Other endpoints associated with asthma exacerbation

##### **Time to first asthma exacerbation**

Time to first asthma exacerbation will be analyzed to explore the extent to which treatment with tralokinumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data including treatment group, OCS dose at baseline and number of exacerbations in the year before the study as covariates. Results of the analysis will be summarized as hazard ratios and 95% confidence intervals comparing tralokinumab with placebo.

Time to first asthma exacerbation will be displayed graphically using a Kaplan-Meier plot. The median time to event will be summarized by randomized treatment, if there is sufficient uncensored data available to calculate these median values.

##### **Proportion of subjects with $\geq 1$ asthma exacerbation**

The proportion of subjects with  $\geq 1$  asthma exacerbation during the 40 week treatment period will be summarized and analyzed using the approach defined for proportion of subjects with  $\geq 50\%$  reduction in final daily average OCS dose, as described in Section 4.2.5.2

#### 4.2.6.6 Emergency room or urgent care visits and hospitalizations due to asthma

AAER that are associated with an ER or UC visit or a hospitalization will be analyzed using a similar Negative binomial model as outlined for the Section 4.2.5.3.

The response variable in the model will be the number of asthma exacerbations that are associated with an ER or UC visit or a hospitalization experienced by a subject, over the 40 week treatment period. The model will include covariates of treatment group, baseline OCS dose at baseline, and number of exacerbations in the year before the study. The logarithm of the subject's corresponding follow-up time in years will be used as an offset variable in the model to adjust for subjects having different exposure times during which the events occur.  
Change from baseline in lung functions

#### 4.2.6.7 Change from baseline in lung functions

##### **Percent change from baseline in lung function variables**

The percent change from baseline in pre-BD FEV<sub>1</sub>, FVC and FEF<sub>25-75%</sub> at Week 12 and Week 40 will be compared between tralokinumab and placebo. A mixed model will be used for the repeated measures (MMRM) with treatment group, visit and baseline OCS dose group as fixed effects and number of asthma exacerbations in the year prior to the study as a covariate. Treatment-by-visit interaction will also be included. The dependent variables will be the



percent change from baseline in each lung function variable at post-baseline protocol-specified visits (up to the EOT visit). A restricted maximum likelihood (REML) approach (with PROC MIXED) will be used.

All subjects with a relevant baseline lung function measurement in the FAS will be included in the respective 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, and the OM option will be used to adjust the coefficients for the LSMEANS to reflect the observed data. The model is:

*Percent change in lung function variable = Treatment group + baseline OCS dose + number of asthma exacerbations in the year prior + visit + treatment\*visit*

Results will be presented in terms of LSMEANS, treatment differences in LSMEANS, 95% confidence intervals and p-values. The treatment comparisons of interest for these variables will be the contrast between tralokinumab and the placebo group at Week 12 and Week 40, but estimates at all visits and overall will be presented. LS MEANS and 95% CIs will also be presented on a graph at each post baseline visit, by treatment group.

Summary statistics for the percent change from baseline at all visits in each lung function variable will be presented by treatment group.

#### **Absolute change from baseline in lung function variables**

The absolute change from baseline in pre-BD FEV<sub>1</sub>, FVC and FEF<sub>25-75%</sub> at Week 12 and Week 40 will be analyzed as described for the percent change on the FAS. Included in the model will also be the baseline lung function result.

Summary statistics for the absolute change from baseline at all visits for each lung function variable will be produced by treatment group.

Absolute and percentage change from baseline will also be listed

#### **4.2.6.8 Asthma symptoms**

The change from baseline in bi-weekly means (daily asthma symptom total score, daytime score, and night-time score) at Week 12 and Week 40 will each be summarized and analyzed using the MMRM approach defined for percent change from baseline in lung function variables, as described in Section 4.2.6.7. Included in the model will also be the baseline bi-weekly mean daily/daytime/night-time asthma symptom score.

LS MEANS and 95% CIs will also be presented graphically for each bi-weekly mean period by treatment group for the total score only.

#### **4.2.6.9 Rescue medication use**

Bi-weekly mean rescue medication use will be summarized and analyzed using the MMRM approach defined for percent change from baseline in lung function variables, as described in Section 4.2.6.7. Included in the model will also be the baseline mean rescue medication use.

The number and percentage of subjects within each treatment group who received rescue medication will be summarized by each bi-weekly period. LS MEANS and 95% CIs will also be presented graphically for the bi-weekly mean periods by treatment group.

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

The change from baseline in bi-weekly mean morning and evening PEF will each be summarized and analyzed using the MMRM approach defined for percent change from baseline in lung function variables, as described in Section 4.2.6.7. Included in the model will also be the baseline morning and evening PEF.

LS MEANS and 95% CIs will also be presented graphically for each bi-weekly mean period by treatment group.

#### **4.2.6.11 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 analyzed using the MMRM approach defined for percent change from baseline in lung function variables, as described in Section 4.2.6.7. Included in the model will also be the baseline bi-weekly mean number (percentage) of nights with awakening due to asthma that required rescue medication.

LS MEANS and 95% CIs will also be presented graphically for the bi-weekly mean periods by treatment group.

#### **4.2.6.12 ACQ-6**

##### **Change in mean score**

Change in mean score from baseline at Week 12 and Week 40 for ACQ-6 (including the individual questions) will be summarized and analyzed using the MMRM approach defined for percent change from baseline in lung function variables, as described in Section 4.2.6.7. Included in the model will also be the baseline ACQ-6 mean score.

LS MEANS and 95% CIs will also be presented graphically at each post baseline visit, by treatment group.

##### **ACQ-6 responder (yes/no)**

Responder variable ACQ-6 (yes/no) will be analyzed using a logistic regression model with responder at Week 40 as the response variable and covariates of treatment, baseline OCS dose, number of asthma exacerbations in the year prior to the study, and baseline ACQ-6 mean score. Subjects who have not completed the Week 40 assessment will be imputed to be non-responders.

##### **ACQ-6 mean score**

The number and percentage of subjects achieving mean ACQ-6  $\leq 0.75$ ,  $> 0.75$  and  $< 1.5$ , and  $\geq 1.5$  as per section 3.3.5 at each scheduled post-randomisation visit will be summarized by treatment.



Additionally, the number and percentage of subjects achieving a change from baseline in mean ACQ-6 score  $\leq -0.5$ ,  $< 0.5$  and  $> -0.5$ , and  $\geq 0.5$  as per Section 3.3.5 at each scheduled post-randomisation visit, will also be summarized by treatment.

The change from baseline to overall post-baseline mean ACQ-6 score and the difference between treatments will be estimated from the MMRM analysis described in Section 4.2.6.7

ACQ-6 mean score, question responses and derived responses will be listed.

#### **4.2.6.13 Asthma specific health-related quality of life**

##### **Change from baseline in AQLQ(S) +12 total score.**

The change in score from baseline for AQLQ(S) +12 (including the domain scores) at Week 12 and Week 40 will be summarized and analyzed using the MMRM approach defined for percent change from baseline in lung function variables, as described in Section 4.2.6.7

Included in the model will also be the baseline AQLQ(S) +12 score.

LS MEANS and 95% CIs will also be presented graphically at each post baseline visit, by treatment group.

##### **AQLQ(S) +12 responder (yes/no)**

Responder variables AQLQ(S) +12 (yes/no) will be analyzed using a logistic regression model with responder at Week 40 as the response variable and covariates of treatment, baseline OCS dose, number of asthma exacerbations in the year prior to the study, and baseline AQLQ(S) +12 total score.

##### **AQLQ(S) +12 total score**

The number and percentage of subjects with AQLQ(S) +12 total score changes  $\geq 0.5$  will be summarized by treatment.

Additionally, the number and percentage of subjects achieving an improvement, no change, or deterioration will be summarized by treatment as per Section 3.3.6.

The change from baseline to overall post-baseline mean AQLQ(S) +12 and the difference between treatments will be estimated using the MMRM approach defined for percent change from baseline in lung function variables, as described in Section 4.2.6.7

AQLQ(S) +12 total score, domain scores and derived responses will be listed.

#### **4.2.6.14 EQ-5D-5L**

The EQ-5D-5L responses from each dimension and the VAS will be summarized by treatment group and listed. The number and percentage responses to each dimension will be summarized by assessment, and shift tables for baseline to last observation during the study will be presented for each dimension. The mean and mean change from baseline to each post-randomisation assessment in VAS will be summarized with descriptive statistics.

#### **4.2.6.15 Health care resource utilization**

The total number events/days will be presented by treatment along with descriptive statistics for the treatment period mean per subject, for all variables listed in Section 3.3.8.

#### **4.2.6.16 WPAI-CIQ**

For each time point at which the WPAI-CIQ is administered, descriptive statistics by treatment will be presented, as described in Section 3.3.9. Responses will also be listed. There will be no imputation for missing values, so where appropriate, the number of missing responses will be included.

#### **4.2.6.17 Analysis of pharmacokinetic variables**

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

Due to the limited sampling schedule, the PK assessment will be primarily based on the observed serum trough (predose) concentrations,  $C_{\text{trough}}$ . Empirical evaluation of potential impact of demographic covariates and ADA on  $C_{\text{trough}}$  may be conducted.

For descriptive statistics of  $C_{\text{trough}}$

- if, at a given time point, 50% or less of the concentrations are non-quantifiable (NQ), the geometric mean, coefficient of variation (CV), arithmetic mean and SD will be calculated by substituting the lower limit of quantification (LLOQ) divided by 2 for values which are NQ.
- if more than 50%, but not all, of the concentrations are NQ, the geometric mean, CV, arithmetic mean and SD will be reported as not calculable (NC)
- if all the concentrations are NQ, the geometric mean and arithmetic mean will be reported as NQ and the CV and SD as NC
- the median, minimum and maximum will also be reported.

The LLOQ of tralokinumab in serum will be 0.100  $\mu\text{g/mL}$ .

The PK data may be merged with those from other clinical studies for a population-based meta-analysis. If performed results of the meta-analysis will be presented in a separate pharmacometrics report outside of the CSR.

Tralokinumab serum concentrations will be tabulated by time along with descriptive statistics.

#### **4.2.6.18 Analysis of Immunogenicity variables**

ADA status (positive vs. negative) at each visit will be summarized by treatment group. Descriptive statistics including number of subjects, mean, SD, median, and range of the actual ADA titers by treatment group and visit, where possible, will be provided. The ADA status

across the study for each subject will also be classified and summarized by treatment group. The association of ADA status across the study with AEs/SAEs and exacerbation data may be evaluated as data allow. In addition, the association of ADA titers ( $\geq$  median titer in positive subjects vs.  $<$  median titer) with AE/SAEs may be evaluated for ADA-positive treated subjects only. A subject will be considered as positive if he/she has a positive ADA for any visit during the study. Otherwise, the subject will be considered as ADA negative. The associations between ADA and AEs/SAEs may be summarized for positive. For ADA summaries at a single time point (e.g. baseline ADA or by visit) the corresponding titer summary will be based on the titer of the positive sample for that particular visit.

For proportions summarizing across visits (e.g. any ADA post-baseline) the corresponding titer summaries will be based on the maximum titer of all positive samples for each subject.

The ADA-positive subjects across the study may also be divided into persistent positive versus transient positive. A subject will be considered as persistent positive if he/she has positive ADAs for at least two consecutive visits (with  $\geq 16$  weeks between the first and last positive value), or positive at the last post-baseline visit. Otherwise, the subject will be considered as transient ADA positive. The associations between ADA and AE/SAEs may be summarized for both persistent positive subjects versus transient positives subjects.

Neutralizing ADA evaluations will be conducted on confirmed ADA positive samples. The test sample is deemed positive or negative for the presence of nAb to tralokinumab relative to a pre-determined (in assay validation), statistically derived cut point.

For ADA, all subjects will be shown in the data listing.

#### **4.2.6.19 Biomarkers**

The change from baseline in biomarkers that may be associated with up-regulation of IL-13 will be explored. Summary statistics and graphical presentations of change from baseline to each assessment will be presented for each biomarker. Possible correlation between biomarker and clinical efficacy will be presented graphically. Biomarkers include IgE, FeNo, and blood Eosinophils.

#### **4.2.7 Sensitivity analyses for missing data**

The primary analysis makes the assumption that a subject's last completed dose before withdrawing from the study is the dose that they remain on to Week 40. It also includes data from subjects who are no longer taking IP. To assess the robustness of the study to missing data and to address the likelihood that the interpretation of data post-discontinuation of IP is likely to be confounded by reduced quality of objective confirmation of deterioration, and by the use of subsequent therapies a number of sensitivity analyses for the primary endpoint and other secondary and exploratory endpoints will be explored.

Six different sensitivity analyses will be included.

##### **4.2.7.1 Multiple Imputation methods**

###### **Copy Reference - Control based imputation**

The first proposed multiple imputation method adopts a missing not at random (MNAR) assumption and assumes that the trajectory of withdrawals from the tralokinumab arm is as bad as that of the placebo subjects. By the end of the study, earlier discontinuers are likely to have worsened, compared to late discontinuers. This model will assume that subjects who withdraw from the study have correlations with future visits similar to subjects in the placebo group. This can be considered more conservative than the approach for the primary analysis by assuming that as soon as subjects withdraw, they begin to worsen immediately. The assumption is that the OCS dose achieved by a subject during the study post withdrawal will tend to be similar to that of a placebo subject with similar covariates and a similar post-baseline history, and that the subject's trajectory will trend towards the average OCS dose of the placebo group as the correlations with the observed post-baseline history weaken. Due to the potentially skewed nature of the data, the observed data will be log transformed before the imputation process, and back transformed before analysis.

The MNAR imputation is achieved by only using appropriate data at each stage of the imputation. Imputation will be done in two steps, the non-monotone (intermediate) missing OCS doses will be imputed first (Markov chain Monte Carlo (MCMC) method is used to partially impute the data using SAS PROC MI ) and then the missing value at each visit will be imputed using a sequential regression method (using MONTONE REG option of SAS PROC MI). To impute at time  $t$ , include only placebo observations up to and including time  $t$ , plus observations from subjects in the tralokinumab arm up to and including time  $t-1$ . This is done for each visit, one at a time using observed data, and missing observations just imputed. Note that in this analysis, placebo missing observations are imputed assuming missing at random (MAR) and follow the pattern of observed placebo observations, and missing observations for the tralokinumab arm are assumed MNAR. The imputation model for the partial imputation will include treatment and baseline OCS dose. 100 imputations will be carried out, and a seed of 221007 will be used. The analysis of each of the imputed dataset will be as described for the primary analysis in Section 4.2.4, these will be combined using SAS procedure PROC MIANALYZE, and results presented as per the primary analysis.

In addition, a tipping point analysis may be performed using the same methodology as above; subjects who withdrew from the study will have their first imputed efficacy score worsened by some amount  $\delta$ . This results in a one-time shift towards a worse value in the outcomes of subjects that withdrew from the study after a given visit. Again, a series of analyses will be performed with a range of increasing deltas for the two arms ( $\delta_P$  and  $\delta_T$  for placebo and tralokinumab group respectively) to identify a tipping point.

In this assessment, the placebo group is assumed to improve after withdrawal and the tralokinumab group is assumed to worsen after withdrawal. Therefore, for OCS dose reduction,  $\delta_P$  will be varied from 1 to 6 dose reductions and  $\delta_T$  will be varied from 1 to 6 dose increases using the dose titration schedule in Table 7. If statistical significance ( $p \leq$  the alpha level used according to the testing strategy described in section 4.1.2) is maintained among the matrix of possible  $\delta$  combinations, the comparison is deemed robust to missing data.

**Copy Reference - Control based imputation – assumptions for missing data depend on reason for discontinuation**

A second multiple imputation analysis will be performed that is identical to the control based imputation except that for subjects who withdraw from the study with primary reason as AE (excluding AEs of exacerbations) the OCS dose will be imputed to be worse (higher) by a constant amount, delta. There is an assumption that if subjects withdraw due to an AE, that this is a sign of a treatment side effect or a treatment failure, which would increase the OCS dose more than the average of subjects in the placebo group.

As with the control based imputation described above, all missing observations will be imputed for the first post baseline visit, and then the delta adjustment will be applied for the visit. Missing observations at the next visit are then imputed using the observed data plus the missing observations just imputed and delta adjusted. This continues until the final visit. The delta adjustment will be applied to each visit after discontinuation of IP. Only the tralokinumab arm is delta adjusted. This is designed to mimic in a realistic fashion the actual carryover of tralokinumab side effects that may be associated with the tralokinumab arm, and may be associated with the decision to withdraw due to an AE. Planned reductions in the study range from 1.25 mg to 5 mg per day at each visit. Based on this, a delta of 3 mg increase per visit for subjects who withdraw with a primary reason of AE will be used.

All other details of this analysis will be as described above for the control based imputation.

#### **4.2.7.2 Single Imputation methods**

##### **Baseline Imputation**

Where a subject withdraws from the study at any point after their baseline assessment and before their Week 40 assessment, the final dose will be imputed to be the subject's baseline OCS dose. This method makes no use of any available data observed post baseline and will be conservative if a subject achieved any benefit from participating in the study for any length of time. Analysis of the primary and secondary variables will be repeated using this imputation. Analyses will be as described in Sections 4.2.4, 4.2.5.1 and 4.2.5.2.

##### **Average Dose**

Where a subject withdraws from the study at any point after their baseline assessment and before their Week 40 assessment, the final dose will be imputed to be the average daily dose that a subject was taking in the 14 days prior to their discontinuation from IP or withdrew from the study (discontinuation from IP, if both apply). The 14 days used for this calculation should not include days where the subject received a temporary burst of systemic corticosteroids. This method will be conservative potentially for subjects who withdraw at an early stage from the study, but who may have later seen a treatment benefit. Analysis of the primary and secondary variables will be repeated using this imputation. Analyses will be as described in Sections 4.2.4, 4.2.5.1 and 4.2.5.2.

#### **4.2.7.3 Additional sensitivity analysis**

Some additional analysis will be added to assess the impact of include data after a subject has discontinued IP and also, for completeness, to aim to include all available data from all subjects.

##### **Repeat of the Primary analysis, excluding data from the time subjects discontinued IP.**

The analysis of the primary and secondary variables will be repeated included data up to the point of IP discontinuation. All data collects from this point will be excluded from the analysis. Analyses will be as described in Sections 4.2.4, 4.2.5.1 and 4.2.5.2, with the definition of final dose as per Section 3.2.1 (disregarding the final bullet point)

##### **Repeat of the Primary analysis, including all available data**

The analysis of the primary and secondary variables will be repeated, including all available OCS dose data. This will include data from subjects that who discontinue IP, but choose (or ultimately migrated to) options 2 and 3 (Section 4.1) for their level of study follow up. This will only be included if there is a sufficient amount of data available that has not been included in the primary and secondary analyses. This will be assessed in advance of the second blind data review. Analyses will be as described in Sections 4.2.4, 4.2.5.1 and 4.2.5.2. Final dose for subjects when this information is not available at Week 40 will be defined as per the relevant bullets in Section 3.2.1.

##### **Repeat of the Primary analysis, adjusting for subjects who had an exacerbation on or after visit 6**

The analysis of the primary variable will be repeated, with percent reduction from baseline in OCS dose will also calculated as follows:

For subjects with no exacerbations recorded following Visit 6, the primary endpoint will be derived as outlined for the primary analysis. For those subjects who do record an exacerbation on or after Visit 6, the final OCS dose used in the percent reduction from baseline calculation will be the OCS dose 1 step higher than the dose at which their first exacerbation started.

The analyses described in Section 4.2.4 will be repeated.

#### **4.2.8 Safety and tolerability**

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

##### **4.2.8.1 Adverse events (AEs)**

AEs will be summarized separately for the treatment and study periods defined in Section 3.4.1.



AEs occurring during the run-in/optimization period, or occurring post-treatment (as per the definition in Section 3.4.1) will be listed, but not summarized.

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, serious 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 SOC/PTs prior to unblinding during the final review of the blinded data review. The total number of AEs in the different AE categories in terms of AE counts will also be presented (i.e., 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. For each PT, the number and percentage of subjects reporting at least one occurrence will be presented i.e., 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 (within a period), the maximum intensity will be taken as the highest recorded maximum intensity for each SOC and PT (the order being mild, moderate, and severe).

The following will also be summarised separately by SOC and PT:

- SAEs
- OAEs
- DAEs
- DAEs causally related to IP
- SAEs leading to discontinuation of IP
- Most comment AE's (frequency of >5%) (by PT only)
- Deaths

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

The approach to identifying possible 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 summarised 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 summarised by MedDRA high level group term, high level term and preferred term by treatment group for the treatment period and study period.

When the FeNO Mid+High subgroup is the primary population, the following summaries will be repeated for subgroups based on  $\text{FeNO} \geq 30$  ppb and  $\text{FeNO} < 30$  ppb: AEs, AEs by PT, SAEs, DAEs, deaths, and hypersensitivity. These summaries will always be repeated for subgroups based on  $\text{FeNO} \geq 37$  ppb and  $\text{FeNO} < 37$  ppb

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 for the treatment period. Rates will be expressed in terms of events per 100 subject-years. Total time at risk will be defined as (the date of last day of IP + 2 weeks) – 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.

Adjudicated events (MACE (major adverse cardiac events) and malignancies) will be summarised by treatment group and listed.

Data from subjects who discontinued IP, regardless of level of follow up chosen will, where possible and relevant, be included in all AE summaries.

#### **4.2.8.2 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 during treatment values, 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. This will be decided during the final review of the blinded data. A diagonal line indicating no change and horizontal and vertical reference lines indicating the limits of the central laboratory reference ranges will also be displayed on the shift plots.

The frequency of changes with respect to normal ranges between baseline and the last observation during the study point will be tabulated. Frequencies of clinically noteworthy



values (using central laboratory 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 (HL) (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 meeting the criteria for HL at any time will 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 during study 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 Negative/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.

#### **4.2.8.3 dECGs**

The Investigator's assessment of the 12-lead dECG (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 dECGs will be summarized by treatment group and visit.

#### **4.2.8.4 Physical Examination**

Shift tables (normal, abnormal (same as Visit 1, new or aggravated), missing/not done) of Visit1 versus last observation during treatment (as defined in Section 3.4.1) 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.

#### **4.2.8.5 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 and baseline and last observation during study, 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.

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.

#### **4.2.8.6 Weight and BMI**

Weight, BMI and height (for adolescents only) will be summarized by absolute value at each visit by treatment group, together with the corresponding changes from baseline.

## **5. INTERIM ANALYSES**

No interim analysis is planned for this study.

An independent Adjudication Committee, blinded to the treatment of the subjects, will evaluate cases of ER or UC visits and hospitalizations, as well as all deaths, to determine whether they are due to asthma or not. The adjudication committee will also review MACE and malignancies occurring after randomization

An independent Data and Safety Monitoring Board (DSMB) will safeguard the interest of adolescent subjects by assessing the safety of the intervention. The DSMB will review safety data on a regular basis as set out in the DSMB charter. The data for review will be outlined in the DSMB charter. The DSMB will have access to individual treatment codes and will be able to merge these with the collected study data while the study is ongoing. For reference, the DSMB will also have access to study data from adults.

An independent review of all potential anaphylaxis/hypersensitivity events will be performed by a clinical expert (external to AZ). Further details of the identification and review process are contained in the Hypersensitivity and Anaphylaxis Process Charter.

## 6. CHANGES OF ANALYSIS FROM PROTOCOL

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

- Section 4.2.8.2: no AZ extended reference ranges have been defined for Tralo so references to this have been removed from this section
- Models used in efficacy analyses will not use age group as a factor because the enrolled population consists almost exclusively of adults.
- Analyses of secondary endpoints that are proportions will be done with logistic regression rather than CMH. This allows the inclusion of an interaction between FeNO subgroup and treatment effect in a natural way that is similar to the primary endpoint and exacerbation rate models.

## 7. REFERENCES

### Hilbe 2011

Hilbe J. M. (2011) “Negative Binomial Regression” Cambridge University Press ISBN: 978-0521-19815-8.

## APPENDIX A

**Table 6** Analysis windows for EQ-5D

<b>Visit</b>	<b>Target Day</b>	<b>Adjusted windows for weekly measures</b>
Baseline (Week 0)	1	1
Week 1	8	2-11
Week 2	15	12-18
Week 3	22	19-25
Week 4	29	26-32
Week 5	36	33-39
Week 6	43	40-46
Week 7	50	47-53
Week 8	57	54-60
Week 9	64	61-67
Week 10	71	68-74

<b>Visit</b>	<b>Target Day</b>	<b>Adjusted windows for weekly measures</b>
Week 11	78	75-81
Week 12	85	82-88
Week 13	92	89-95
Week 14	99	96-102
Week 15	106	103-109
Week 16	113	110-116
Week 17	120	117-123
Week 18	127	124-130
Week 19	134	131-137
Week 20	141	138-144
Week 21	148	145-151
Week 22	155	152-158
Week 23	162	159-165
Week 24	169	166-172
Week 25	176	173-179
Week 26	183	180-186
Week 27	190	187-193
Week 28	197	194-200
Week 29	204	201-207
Week 30	211	208-214
Week 31	218	215-221
Week 32	225	222-228
Week 33	232	229-235
Week 34	239	236-240
Week 35	246	241-249
Week 36	253	250-256
Week 37	260	257-263
Week 38	267	264-270
Week 39	274	271-277
Week 40	281	278-284

**Table 7 OCS dose titration schedule recommended during the reduction phase (V12-V20)<sup>a,b</sup>**

<b>Optimized dose at V6 W0</b>	<b>Visit 12 W12</b>	<b>Visit 14 W16</b>	<b>Visit 16 W20</b>	<b>Visit 18 W24</b>	<b>Visit 20 W28</b>
30	25	20	15	10	7.5
27.5	22.5	17.5	12.5	7.5	5
25	20	15	10	7.5	5
22.5	17.5	12.5	7.5	5	2.5
20	15	10	7.5	5	2.5
17.5	12.5	7.5	5	2.5	1.25
15	10	7.5	5	2.5	1.25
12.5	7.5	5	2.5	1.25	0
10	7.5	5	2.5	1.25	0
7.5	5	2.5	1.25	0	0

<sup>a</sup> – All doses expressed in mg/day

<sup>b</sup> - Titration schedule should be followed when the titration criteria are met at every titration visit (not applicable for Visit 12, see Section 4.2.2 of the CSP). A daily dose of 1.25 mg may be administered as 2.5 mg every other day.