AstraZeneca

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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 dependent Asthma (TROPOS)

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Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

International Co-ordinating Investigator: [redacted]

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The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
1	11 May 2015		
2	7 August 2015		
3	22 February 2016		
Administrative Change No.	**Date of Administrative Change**	**Local Administrative Change No.**	**Date of Local Administrative Change**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

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 dependent Asthma (TROPOS)

International Co-ordinating Investigator: [redacted]

Study site(s) and number of subjects planned

Approximately 120 subjects will be randomized at approximately 75 study centers worldwide.

Study period		Phase of development
Estimated date of first subject enrolled	Q1 2015	3
Estimated date of last subject completed	Q4 2017	3

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 in adult and adolescent subjects with oral corticosteroid dependent asthma.

Approximately 120 subjects will be randomized to tralokinumab or placebo (1:1) globally from about 75 study centers. All subjects will be stratified at randomization by age group (adults versus adolescents). Adult subjects will also be stratified at randomization by the baseline oral corticosteroid dose (≤ 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 oral corticosteroid medication history, enter either:

- a 2-week run-in period (if there has been a documented failure of oral corticosteroid dose reduction within 6 months prior to Visit 1, and after discussion with the sponsor study physician) (see section 4.1.1 and 4.1.2), or
- a 2-week run-in period plus an 8-week optimization period to establish a minimum effective dose of the prescribed oral corticosteroid (established by dose titration every two weeks).

Subjects who fulfill the eligibility criteria will be randomized to a 40-week treatment period. The last dose of tralokinumab or placebo will be given at week 38 with the end of treatment visit at week 40. Subjects will be maintained on their currently prescribed inhaled corticosteroid plus long-acting beta-2 agonist and any additional asthma controller medication, without change, from enrolment, throughout the run-in/optimization and treatment periods.

There are three phases in the 40-week treatment period following randomization where subjects will be administered study drug.

- Induction phase – from week 0 to up to week 12 where subjects should remain on their optimized oral corticosteroid dose.

- Oral corticosteroid reduction phase – from week 12 up to week 32, oral corticosteroid dose reduction can be started at week 12 with the possibility of dose titration every 4 weeks.

- Maintenance phase – after the week 32 visit to week 40, subjects should remain on the oral corticosteroid dose reached at week 32 or remain on complete oral corticosteroid elimination.

Post treatment safety follow up visits will be performed at Week 44 and Week 54.

Objectives

Primary Objective:	**Outcome Measures:**
To evaluate the effect of tralokinumab compared to placebo in reducing the prescribed, oral corticosteroid maintenance dose in adult and adolescent subjects with asthma requiring chronic treatment with maintenance oral corticosteroids in addition to inhaled corticosteroid plus long-acting β2-agonist	**Primary outcome variable:** Percent change from baseline in the daily, average, oral corticosteroid dose at week 40 post randomization while not losing asthma control **Primary outcome measure:** Percent difference vs. placebo at Week 40 post randomization

Secondary Objectives:	**Outcome Measures:**
To evaluate the effect of tralokinumab compared to placebo on the proportion of subjects with the prescribed, oral corticosteroid maintenance dose ≤5 mg in adult and adolescent subjects with asthma requiring chronic treatment with maintenance oral corticosteroids in addition to inhaled corticosteroid plus long-acting β2-agonist	Difference vs. placebo in the proportion of subjects with final daily average oral corticosteroid dose ≤5 mg at Week 40 post randomization
To evaluate the effect of tralokinumab compared to placebo on the proportion of subjects with at least 50% reduction in their prescribed, oral corticosteroid maintenance dose in adult and adolescent subjects with asthma requiring chronic treatment with maintenance oral corticosteroids in addition to inhaled corticosteroid plus long-acting β2-agonist	Difference vs. placebo in the proportion of subjects with ≥50% reduction in average daily oral corticosteroid dose at Week 40 post randomization

Safety Objective:	**Outcome Measures:**
To evaluate the safety and tolerability of tralokinumab	– Adverse Events/Serious Adverse Events – Vital signs – Digital electrocardiograms – Clinical chemistry/haematology/urinalysis – Physical examinations

Exploratory Objectives:	**Outcome Measures:**
To evaluate the effect of tralokinumab versus placebo in overall oral corticosteroid exposure	Overall oral corticosteroid exposure measured by the area under the dose curve
To evaluate the effect of tralokinumab versus placebo in the proportion of subjects that have decreased their daily average prescribed, oral corticosteroid dose	Change from baseline daily average oral corticosteroid dose classified as: 1. 100% reduction (no OCS) 2. ≥ 90% to < 100% reduction 3. ≥ 75% to < 90% reduction 4. ≥ 50% to < 75% reduction 5. > 0% to < 50% reduction 6. no change in average OCS dose 7. increased average OCS dose
To evaluate the effect of tralokinumab compared with placebo on asthma exacerbations.	**Outcome variable:** The annualised asthma exacerbation rate up to Week 40. **Outcome measure**: Asthma exacerbation rate reduction
To evaluate the effect of tralokinumab compared with placebo on lung function	**Outcome variables:** Percent change from baseline in pre-bronchodilator forced expiratory volume in 1 second, Forced Vital Capacity and Forced Expiratory Flow between 25% and 75% of the Forced Vital Capacity **Outcome measure:** Percent difference vs. placebo at Week 12 and 40

To evaluate the effect of tralokinumab compared with placebo on asthma symptoms and other asthma control metrics	**Outcome variables:** - Change from baseline in bi-weekly mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily Diary). - Change from baseline in rescue medication use - Change from baseline in home peak expiratory flow (morning and evening) - Change from baseline in the number of night-time awakening due to asthma - Change from baseline in Asthma Control Questionnaire 6 **Outcome measure:** Mean difference vs. placebo at Week 12 and Week 40
To evaluate the effect of tralokinumab compared with placebo with regards to asthma specific health-related quality of life	**Outcome variable:** Change from baseline in Standardised Asthma Quality of Life Questionnaire for 12 Years and Older total score **Outcome measure:** Mean difference vs. placebo at Week 12 and Week 40
To evaluate the effect of tralokinumab compared with placebo with regards to health related quality of life.	**Outcome variable:** European Quality of Life 5 Dimension 5 Level Questionnaire **Outcome measure:** Mean difference vs. placebo at Week 12 and Week 40
To evaluate the effect of tralokinumab compared with placebo with regards to health care resource utilization and productivity loss due to asthma	**Outcome variables:** – Asthma specific resource utilization (e.g., unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) – Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire scores **Outcome measure:** Mean difference vs. placebo at Week 12 and Week 40

To evaluate the pharmacokinetics and immunogenicity of tralokinumab	**Outcome variables:** – Pharmacokinetic parameters: C_{trough} at steady-state – Immunogenicity outcome variables: incidence rate of positive anti-drug antibodies and characterization of their neutralizing potential
To evaluate the change from baseline of biomarkers that may be associated with up-regulation of interleukin-13 To evaluate the relationship between baseline biomarkers and the effect of tralokinumab on oral corticosteroid dose reduction and clinical efficacy To evaluate the impact of oral corticosteroid optimization on biomarkers	Biomarkers will include: – Periostin – Dipeptidyl peptidase-4 – Blood eosinophils – Total serum Immunoglobulin E – Fractional exhaled nitric oxide Other specific blood biomarkers may also be analyzed.

Target subject population

Male and female adults and adolescents, 12-75 years of age inclusive with diagnosed asthma willing to provide informed consent and requiring continuous treatment with inhaled corticosteroids (≥ 500 mcg fluticasone dry power formulation equivalents total daily dose) plus long-acting β2-agonist and chronic treatment with maintenance oral corticosteroid therapy.

Duration of treatment

Following an initial enrolment (Visit 1), depending on recent asthma and oral corticosteroid medication history, subjects will enter either a 2 week run-in period or a 2-week run-in period plus an 8-week oral corticosteroid dose optimization period. The first dose of tralokinumab/placebo will be administered at Week 0. Subjects will receive tralokinumab or placebo every two weeks over a 40-week treatment period.

Investigational product, dosage and mode of administration

Tralokinumab 300 mg (150 mg/mL), or placebo, will be administered to subjects via subcutaneous injection using 2 accessorized pre-filled syringes at the study site.

Statistical methods

The primary analysis of the efficacy endpoints will include all data captured during the double blind, treatment period (intent-to-treat approach).

The primary efficacy objective will be evaluated through the null hypothesis test H0: Difference in percentage reduction in the prescribed, oral corticosteroids (tralokinumab-placebo) equals 0 vs. H1: difference not equal to 0. The test will be based on an analysis of covariance model. Covariates and factors included in the model will include at least treatment, age group and baseline oral corticosteroid dose.

For binary variables based on oral corticosteroid dose, the proportion in the tralokinumab group will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for age group and baseline oral corticosteroid dose. Continuous variables related to lung function, symptoms, health-related quality of life and Asthma Control Questionnaire-6 will primarily be analyzed using a repeated measures analysis approach including at least treatment, baseline value and stratifying variables as the explanatory variables.

Asthma exacerbation rates will be analyzed using negative binomial models with the covariates of treatment, stratifying variables and number of exacerbations in the year before the study.

The sample size is based on the primary endpoint; percentage change in oral corticosteroid dose. Given an assumed standard deviation of 80% it is estimated that 55 subjects in each treatment arm will be sufficient to achieve at least 90% power to detect a true difference versus placebo of 50% using a two-sided test at 5% significance level.

The results for the exploratory variables will be summarized using descriptive statistics and confidence intervals by treatment group.

All safety parameters will be analyzed descriptively. The safety analyses will be based on the safety analysis data set, defined as all subjects who received at least one dose of investigational product.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-drug antibody
AE	Adverse Event
AAER	Annual Asthma Exacerbation Rate
AERR	Asthma Exacerbation Reduction Rate
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APFS	Accessorized Pre-filled Syringe
AQLQ(S)+12	Standardised Asthma Quality of Life Questionnaire for 12 Years and Older
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS/ERS	American Thoracic Society/European Respiratory Society
BD	Bronchodilator
β-HCG	Beta-Human Chorionic Gonadotropin
BUN	Blood Urea Nitrogen
CO_2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CSA	Clinical Study Agreement
CSR	Clinical Study Report
DAE	Discontinuation of Investigational Product due to Adverse Event
dECG	Digital Electrocardiogram
DPP4	Dipeptidyl Peptidase-4
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)

Abbreviation or special term	Explanation
eCRF	Electronic Case Report Form
ED	Emergency Department
ER	Emergency Room
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome device
EQ-5D-5L	European Quality of Life - 5 Dimensions - 5 Level
EXACA	Module name of case report form to capture asthma exacerbations
FE_{NO}	Fractional Exhaled Nitric Oxide
$FEF_{25-75\%}$	Forced Expiratory Flow between 25% and 75% of the Forced Vital Capacity
FEV_1	Forced Expiratory Volume in 1 second
FSH	Follicle-Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GINA	Global Initiative for Asthma
GLI	The Global Lung Function Initiative
GMP	Good Manufacturing Practice
Grand	Randomization Code Generator - Computerized System
HCP	Healthcare professional
HIV	Human Immunodeficiency Virus
HRU	Healthcare resource utilisation
IATA	International Air Transport Association
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICI	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
ICS	Inhaled Corticosteroids
IgE	Immunolglobulin E

Abbreviation or special term	Explanation
IL	Interleukin
IL-13	Interleukin-13
IP	Investigational Product
IPD	Investigational product discontinuation
IRB	Institutional Review Board
ISF	Investigator Study File
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-Acting β_2-Agonist
LTRA	Leukotriene Receptor Antagonists
MAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
nAB	Neutralizing Antibodies
OAE	Other significant adverse events
OCS	Oral Corticosteroids
PD	Pharmacodynamic
PEF	Peak Expiratory Flow
PK	Pharmacokinetic(s)
PNV	Predicted Normal Value
PRO	Patient Reported Outcome
PT	Preferred Term
Q2W	Every 2 Weeks
Q4W	Every 4 Weeks
SABA	Short-Acting β2-Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOC	System Organ Class

Abbreviation or special term	Explanation
Th2	T Helper 2 Cells
TLC	Total Lung Capacity
ULN	Upper Limit of Normal
UNS	Unscheduled
WBDC	Web Based Data Capture
WOCBP	Women of Childbearing Potential
WPAI+CIQ	Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Asthma is a syndrome characterized by airway inflammation, reversible airway obstruction and airway hyperresponsiveness, with a global prevalence of approximately 300 million patients (GINA 2014).

Approximately 5% to 10% of asthma patients have severe asthma, many of whom may be inadequately controlled by inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABA) in combination with additional controller therapies (Bateman et al 2010). These patients are at risk of asthma exacerbations, have a large medical need, and represent the greatest economic burden (Accordini et al 2006).

The observed variability in clinical response to currently available asthma therapies appears to be related, in part, to distinctive inflammatory phenotypes (Wenzel 2012). There is considerable evidence that interleukin-13 (IL-13) is a key mediator in the pathogenesis of asthmatic disease. IL-13 is secreted predominantly by CD4+ T-helper 2 (Th2) cells and IL-13 receptors are expressed on a number of cell types including those involved in the pathogenesis of asthma (Hershey 2003). There is evidence to support that IL-13 can increase development of airway hyperresponsiveness (Wardlaw et al 1988), potentiate bronchoconstriction (Grunstein et al 2002), increase the number of mucus-secreting cells and promote airway fibrosis in asthma (Wills-Karp et al 1998).

Tralokinumab is a human recombinant monoclonal antibody (MAb) of the immunoglobulin G4 subclass that specifically binds human IL-13, blocking interactions with the IL-13 receptor. Tralokinumab is in development for the treatment of severe asthma. A phase 2a study (MI-CP199) provided evidence of improvement of lung function, forced expiratory volume in 1 second (FEV_1), following the addition of subcutaneous (SC) tralokinumab to standard asthma controller medications. Doses of 300 and 600 mg every 2 weeks of tralokinumab both resulted in comparable improvements in FEV_1 that were greater than that observed with a 150 mg dose (Piper et al 2013). Because low pre-bronchodilator (BD) FEV_1 has been identified as a strong independent predictor of subsequent asthma exacerbations, it is plausible that the addition of tralokinumab will reduce the rate of asthma exacerbations, improving lung function (Reddel et al 2009).

In a phase 2b (CD-RI-CAT-354-1049) study with tralokinumab in adults with uncontrolled, severe asthma requiring high dose ICS and LABA, the efficacy and safety of 2 different treatment regimens of tralokinumab (300 mg every 2 weeks (Q2W) or, 300 mg Q2W for 12 weeks, followed by a 300 mg every 4 weeks (Q4W) maintenance dosing [Q2/4W]) vs. placebo, was evaluated over a treatment period of 52 weeks. The primary endpoint for this study was the annualised asthma exacerbation rate (AAER) over 52 weeks, with secondary endpoints including pulmonary function, patient reported outcomes, including asthma symptoms. In the overall intent-to-treat (ITT) phase 2b population, an increase from baseline

in pre-BD FEV_1 to the end of treatment was seen with the Q2W dosing regimen, but not with the Q2/4W dosing regimen.

In this phase 2b study, a subpopulation reversible to bronchodilators on study entry (FEV_1 reversibility ≥ 12% and ≥200 ml in FEV_1) had an observed AAER reduction that was greater for the tralokinumab 300 mg Q2W cohort versus the Q2/4W cohort. A further reduction of AAER was observed in a subgroup of reversible subjects with high (> median) serum periostin or dipeptidyl peptidase-4 (DPP4), biomarkers induced by IL-13. The AAER efficacy signal observed in this biomarker-positive and reversible sub-group appeared to be somewhat attenuated in the presence of oral corticosteroid (OCS) co-medication (approximately 17% of patients in the ITT population were on OCS), although there was no clear explanation for this (for further details see the Investigator's brochure). However, since patients who required treatment with maintenance OCS are a distinct population, in the Phase III program they will be studied in this separate OCS sparing study.

OCS are effective agents for controlling airway inflammation in asthma and are indicated for severe persistent asthma, as outlined in Step 5 of the Global Initiative for Asthma (GINA 2014) guidelines. Since long-term treatment with OCS use can result in adverse reactions such as osteoporosis, diabetes, cataract and growth retardation in children, a major objective in this population is to reduce their overall exposure to OCS thereby minimising adverse events.

IL-13 over-expression as detected in sputum, in peripheral blood-derived T cells and in bronchial biopsy samples is a signature of patients with severe asthma (Saha et al 2008, Siddiqui et al 2009). Moreover, in severe, asthmatic patients who have an active IL-13 axis, cessation of OCS treatment caused an increase in IL-13 expression, which was not observed in patients who did not have an active IL-13 axis (MedImmune data on file). Therefore, patients who have an active IL-13 axis, as defined by high periostin and/or DPP4 levels, including patients on maintenance OCS, may benefit from treatment with tralokinumab. Given the need to reduce the requirement of OCS in patients with severe asthma, treatments that may allow tapering of OCS without loss of control are needed. To date, no clinical study has been conducted in severe asthmatic patients on maintenance OCS with agents that attenuate IL-13 signaling in a regime. The purpose of the present study is therefore to demonstrate the ability of tralokinumab versus placebo in reducing OCS use in adults and adolescents with asthma requiring treatment with maintenance OCS in combination with ICS/LABA with or without other asthma controller therapy.

1.2 Rationale for study design, doses and control groups

This is a global study designed to evaluate the efficacy and safety of a fixed 300 mg dose of tralokinumab administered subcutaneously every 2 weeks in asthma subjects who are on maintenance OCS and ICS/LABA therapy, with or without additional asthma controller(s). Subjects will be dosed every two weeks throughout a 40 week treatment period.

The primary efficacy measure will be based on the percentage change from baseline in the prescribed, daily, average OCS dose at week 40 post randomization while not losing asthma control. In order to avoid bias, the study is to be randomized and double-blinded, with

stratification by age group (adults versus adolescents) and for adult subjects only by the baseline OCS dose (≤ 10 mg versus >10 mg prednisone or prednisolone). Analysis of data from both the phase 2a study MI-CP199 and the phase 2b study (CD-RI-CAT-354-1049), has demonstrated a clinically relevant effect on FEV_1 from tralokinumab 300 mg Q2W. In contrast, only limited, if any, improvement was observed with 150 mg Q2W (in study MICP199) or 300 mg Q2/4W (in study CD-RI-CAT-354-1049). Furthermore, an effect on AAER was observed with the 300 mg Q2W dosing regimen, but not with the Q2/4W dosing regimen in study CD-RI-CAT-354-1049. Therefore the dose of 300 mg Q2W has been selected for evaluation in this study.

Pharmacokinetic (PK) evaluations in adolescents with asthma confirm that the same dose as for adults is applicable and since it is expected that adolescent subjects (12-17 years of age) will respond similarly to adults, adolescents will therefore be included as part of the study population.

1.3 Benefit/risk and ethical assessment

There are few treatment options for subjects whose asthma remains uncontrolled on ICS/LABA (GINA 2014). The evidence base for oral add-on therapies (i.e. OCS, leukotriene inhibitors (LTRAs), and xanthenes) is limited. Anti-immunoglobulin E (IgE) therapy (ie, omalizumab) improves control in a subset of subjects with severe asthma associated with IgE-mediated allergy to a perennial allergen. Hence, new therapies are needed for asthma management in subjects who remain uncontrolled on standard of care.

IL-13 is targeted as it plays a role in the allergic/Th2 type response which is a signature of asthma. An anti-IL-13 treatment may therefore be useful in treatment of asthma. Data from phase 2 studies support this notion. In the 24 week phase 2a study (MI-CP199) tralokinumab at a dose of 300 mg SC every 2 weeks (the dose proposed for the phase 3 programme) improved FEV_1 when added to standard asthma controller medications. In addition the efficacy of tralokinumab has been studied in a 1 year long phase 2b study (CD-RI-CAT-354-1049) targeting adult subjects whose asthma was poorly controlled by high dose ICS/LABA. In that study, tralokinumab at a fixed dose of 300 mg SC every other week produced improvements in multiple metrics of asthma control, including the AAER, lung function, Asthma Control Questionnaire-6 (ACQ-6) scores, and symptoms, in a subpopulation who demonstrated reversibility of FEV_1 upon study entry.

Approximately 520 subjects with asthma have so far been exposed to tralokinumab at various doses and for different periods of time. The 1 year long phase 2b study has contributed 301 of these subjects with 140 of them receiving 300 mg every other week. In all studies conducted so far, tralokinumab has been well tolerated, and no safety concerns have been identified.

However, because it is believed that the Th2 response may be of importance in the defense against helminthic parasitic infections, a theoretical risk for such infestations exists. IL-13 may also play a role in regulating tumours (Hallett et al 2012), and although evidence for this is scarce and inconclusive, this theoretical risk needs to be considered. In conjunction with the

performance of routine pharmacovigilance activities risk minimization measures therefore include the exclusion of subjects with untreated parasitic infection and active or recent malignancy.

As with all biologics therapies, anti-drug antibodies (ADA), including neutralizing antibodies (nAb), may develop. Development of ADA to tralokinumab has been rare in the phase 1 and 2 studies conducted thus far (<1% overall). Theoretical risks due to development of ADA include decreased drug efficacy and hypersensitivity reactions (eg, anaphylaxis or immune complex disease) and observation following administration of tralokinumab is therefore mandated.

Pharmacokinetic modelling suggests that exposure to tralokinumab is slightly higher in adolescents (12-17 years of age) than that in adults; however, considering the overall variability of tralokinumab PK, and the absence of safety findings at doses at or above 300 mg every other week in the phase 2 studies, dose adjustment is not considered to be required for subjects in this age group.

In summary, the efficacy and safety data obtained to date support the continued clinical development of tralokinumab in adult and adolescent subjects with uncontrolled asthma

A detailed assessment of the risk/benefit of tralokinumab in subjects with asthma is given in the Investigator's brochure (IB).

1.4 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 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 75 centers. All subjects will be stratified at randomization by age group (adults versus adolescents). Adult subjects will also be stratified at randomization by the baseline oral corticosteroid dose (≤ 10 mg versus > 10 mg prednisone or prednisolone).

Subjects will be administered 300 mg tralokinumab (2 x 150mg, 1mL injections) or placebo (2 x 1mL injections) every 2 weeks using pre-filled syringes over a 40-week treatment period.

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) (see section 4.1.1 and 4.1.2), 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 noted in section 5.1.2.

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 in a 1:1 ratio to receive tralokinumab or placebo over 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 FEV1; a 20 week OCS dose reduction phase to reach the lowest possible dose based on the titration schedule (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.

- 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.

Post-treatment safety follow up visits will be performed at Week 44 and Week 54.

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

An independent Adjudication Committee, blinded to the treatment of the subjects, will evaluate cases of ER or urgent care visits and hospitalizations, as well as all deaths, to determine whether they are due to asthma or not. For completeness, the adjudication committee will also be tasked with reviewing cardiovascular, cerebrovascular and malignant adverse events occurring after randomisation. 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 also have access to study data from adults.

Figure 1 Study flow chart (subjects with documented failure of OCS reduction within 6 months prior to Visit 1)

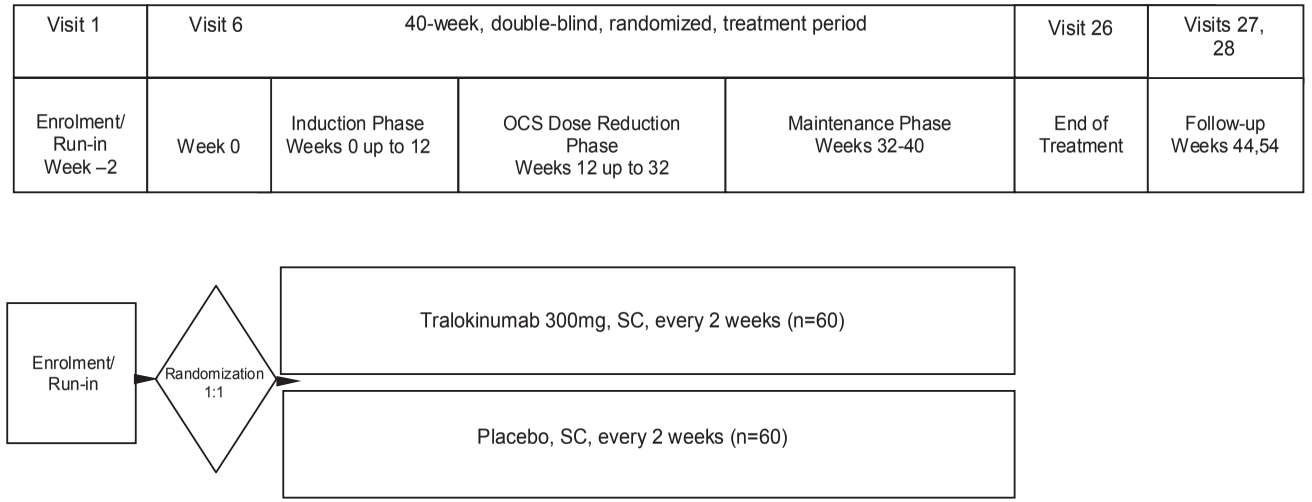
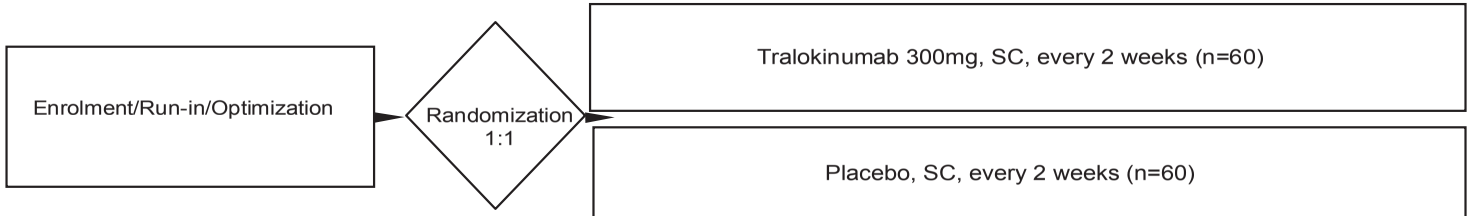


Figure 2 Study flow chart (subjects undergoing dose optimization)

Visit 1	Visit 2-Visit 5*	Visit 6	40-week, double-blind, randomized, treatment period			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	Maintenance Phase Weeks 32-40	End of Treatment	Follow-up Weeks 44,54



***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.**

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measures:
To evaluate the effect of tralokinumab compared to placebo in reducing the prescribed, OCS maintenance dose in adult and adolescent subjects with asthma requiring chronic treatment with maintenance OCS in addition to ICS/LABA	**Primary outcome variable:** Percent change from baseline in the daily, average, OCS dose at week 40 post randomization while not losing asthma control **Primary outcome measure:** Percent difference vs. placebo at Week 40 post randomization

2.2 Secondary objectives

Secondary Objectives:	Outcome Measures:
To evaluate the effect of tralokinumab compared to placebo on the proportion of subjects with the prescribed, OCS maintenance dose ≤5 mg in adult and adolescent subjects with asthma requiring chronic treatment with maintenance OCS in addition to ICS/LABA	Difference vs. placebo in the proportion of subjects with final daily average OCS dose ≤5 mg at Week 40 post randomization
To evaluate the effect of tralokinumab compared to placebo on the proportion of subjects 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/LABA	Difference vs. placebo in the proportion of subjects with ≥50% reduction in average daily OCS dose at Week 40 post randomization

2.3 Safety objectives

Safety Objective:	**Outcome Measures:**
To evaluate the safety and tolerability of tralokinumab	– AE/SAEs – Vital signs – dECG – Clinical chemistry/haematology/urinalysis – Physical examinations

2.4 Exploratory objectives

Exploratory Objectives:	**Outcome Measures:**
To evaluate the effect of tralokinumab versus placebo in overall OCS exposure	Overall OCS exposure measured by the area under the dose curve
To evaluate the effect of tralokinumab versus placebo in the proportion of subjects that have decreased their daily average prescribed, OCS dose	Change from baseline daily average oral corticosteroid dose classified as: 1. 100% reduction (no OCS) 2. ≥ 90% to < 100% reduction 3. ≥ 75% to < 90% reduction 4. ≥ 50% to < 75% reduction 5. > 0% to < 50% reduction 6. no change in average OCS dose 7. increased average OCS dose
To evaluate the effect of tralokinumab compared with placebo on asthma exacerbations.	**Outcome variable:** The AAER up to Week 40. **Outcome measure:** Asthma exacerbation rate reduction
To evaluate the effect of tralokinumab compared with placebo on lung function	**Outcome variable:** Percent change from baseline in pre-bronchodilator FEV_1, Forced Vital Capacity (FVC) and Forced Expiratory Flow $(FEF)_{25-75\%}$ **Outcome measure:** Percent difference vs. placebo at Week 12 and 40

To evaluate the effect of tralokinumab compared with placebo on asthma symptoms and other asthma control metrics	**Outcome variables:** - Change from baseline in bi-weekly mean daily asthma symptom score (combined daytime and night-time score as captured in the Asthma Daily Diary). - Change from baseline in rescue medication use - Change from baseline in home peak expiratory flow (morning and evening) - Change from baseline in the number of night-time awakening due to asthma - Change from baseline in ACQ-6 **Outcome measure:** Mean difference vs. placebo at Week 12 and Week 40
To evaluate the effect of tralokinumab compared with placebo with regards to asthma specific health-related quality of life	**Outcome variable:** Change from baseline in Standardised AQLQ(S) + 12 **Outcome measure:** Mean difference vs. placebo at Week 12 and Week 40
To evaluate the effect of tralokinumab compared with placebo with regards to health related quality of life.	**Outcome variable:** EQ-5D-5L **Outcome measure:** Mean difference vs. placebo at Week 12 and Week 40
To evaluate the effect of tralokinumab compared with placebo with regards to HRU and productivity loss due to asthma	**Outcome variables:** – Asthma specific resource utilization (e.g., unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) – WPAI+CIQ scores **Outcome measure:** Mean difference vs. placebo at Week 12 and Week 40

To evaluate the pharmacokinetics and immunogenicity of tralokinumab	**Outcome variables:** – PK parameters: C_{trough} at steady-state – Immunogenicity outcome variables: incidence rate of positive ADA and characterization of their neutralizing potential
To evaluate the change from baseline of biomarkers that may be associated with up-regulation of IL-13 To evaluate the relationship between baseline biomarkers and the effect of tralokinumab on OCS dose reduction and clinical efficacy To evaluate the impact of OCS optimization on biomarkers	Biomarkers will include: – Periostin – DPP-4 – Blood eosinophils – Total serum IgE – FE_{NO} Other specific blood biomarkers may also be analyzed.

3. SUBJECT SELECTION, ENROLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study, subjects must fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures for subjects who are at, or over the age of majority (as per local law). For subjects less than the age of majority, in addition to the subject providing informed assent, the subject's legal guardian must also provide their informed consent.

2. Female or male, ages 12 to 75 years, inclusively at time of enrolment (Visit 1). For those countries where local regulations permit enrolment of adults only, subject recruitment will be restricted to those who are ≥18 years.

3. Women of childbearing potential (WOCBP) (after menarche) and all adolescent females must use a highly effective form of birth control (confirmed by the Investigator). Highly effective forms of birth control includes: true sexual abstinence, a vasectomised sexual partner, Implanon® , female sterilization by tubal occlusion, any effective intrauterine device/system (IUD/IUS), Depo-Provera™ injections, oral contraceptive, and Evra Patch ™ or Nuvaring™. WOCBP must agree to use highly effective method of birth control, as defined above, from enrolment (Visit 1), throughout the study duration and within 16 weeks after last dose of investigational product (IP), and have a negative serum pregnancy test result at Visit 1.

   Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

   - Women <50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels in the postmenopausal range.

   - Women ≥50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.

4. Weight of ≥ 40 and <150 kg at enrolment (Visit 1).

5. Documented physician-diagnosed asthma for at least 12 months prior to enrolment (Visit 1) with the subject having received an asthma controller regimen requiring treatment with medium-to-high dose ICS for at least 6 of the 12 months prior to enrolment (Visit 1). In addition, subjects must have used physician prescribed ICS (at a total daily dose ≥ 500µg fluticasone propionate via dry powder inhaler or equivalent delivered dose) that has been taken at a stable dose for at least 3 months prior to enrolment (Visit 1).

6. Documented treatment with ICS at a total daily dose corresponding to ≥ 500µg fluticasone propionate dry powder formulation equivalents and a LABA for at least 3 months prior to Visit 1. The ICS and LABA can be parts of a combination product, or given by separate inhalers.

   - In order to aid the assessment, ICS equivalents for high-dose and medium-dose fluticasone propionate dry powder, are presented in Appendix E. The Investigator will assess the subject's total daily ICS dose and determine that it corresponds to ≥ 500µg fluticasone propionate dry powder formulation

equivalents. If the subject is on two or more different types of ICS, these can form parts of an addition, and the sum, however approximate, will be assessed.

7. Subjects must have received OCS for the treatment of asthma for 6 months prior to Visit 1 and on a stable OCS dose of between ≥ 7.5 to ≤ 30mg (prednisone or prednisolone equivalent) daily or daily equivalent for at least one month prior to enrolment (Visit 1).

    - Subjects with a documented failure of OCS dose reduction within 6 months prior to Visit 1 can omit Visits 2 to 5 (after discussion with the sponsor study physician) and complete a shorter 2 week run-in prior to Visit 6 (randomization visit)

    - Failed attempts at OCS dose reduction are those that resulted in a clinical deterioration or reduced lung function attributed to asthma, demonstrated by documented occurrence of at least one of the following:

        - Pre-BD FEV_1 < 80% of personal baseline
        - Morning peak expiratory flow (PEF) < 80% of personal baseline
        - Night time awakenings increase of > 50% of mean personal baseline
        - Rescue medication use, for example salbutamol > 4 puffs/day above mean personal baseline
        - Requirement for an OCS burst (large temporary increase) to treat an asthma exacerbation provoked by steroid reduction

    Subjects without a documented failure of OCS dose reduction within the previous 6 months must complete the 2-week run-in period plus the 8-week dose optimization period prior to Visit 6 (randomization visit). See section 4.1.2 for details.

8. Additional maintenance asthma controller medications are allowed according to standard practice of care. These medications must be stable for 3 months prior to Visit 1. Furthermore, after randomization, the subject's background maintenance medication for asthma shall remain unchanged throughout the study.

9. At enrolment (Visit 1) the subject must have a pre-BD FEV_1 of <80% (<90% for patients 12 to 17 years of age) of their predicted normal value (PNV). If this criterion is not met at Visit 1, the criterion must be met at Visit 2 or Visit 6 (if a subject is not required to undergo dose optimization). Prior to the lung function measurement, the subject should withhold theophylline and their BD for the effect duration specific to the BD (see 5.1.4 and Appendix G).

10. A post-BD reversibility in FEV_1 of $\geq$12% at enrolment (Visit 1) or documented reversibility within 6 months prior to Visit 1 with available source documentation and after discussion with the sponsor study physician. If there is no evidence of a documented reversibility within 6 months prior to Visit 1 or this criterion is not met at Visit 1, the criterion must be met at Visit 2 or Visit 6 (if a subject is not required to undergo dose optimization). Prior to the lung function measurement, the subject should withhold theophylline and their BD for the effect duration specific to the BD (see 5.1.4 and Appendix G).

Prior to randomization at Visit 6, subjects should fulfil the following inclusion criteria:

11. For WOCBP (including all adolescents) only: have a negative urine pregnancy test prior to administration of the IP.

12. No requirement for a change in the subjects ICS/LABA, other asthma controller medications and/or the requirement to add asthma controller medications during the run-in or run-in/optimization periods.

13. For all subjects (those proceeding directly to run-in and those undergoing dose optimization), the optimized OCS dose reached at least two weeks prior to randomization.

14. Minimum 70% compliance with OCS use.

    - For example, 10 out of the 14 days between each visit in the run-in/optimization periods, prior to randomization as reported by the subject in the eDiary.

15. Ability to perform acceptable inhaler, peak flow meter, and spirometry techniques.

16. Minimum 70% compliance with both the usual asthma controller (ie ICS/LABA and any other asthma controller medications).

    - For example, 10 out of the 14 days between each visit in the run-in/optimization periods, prior to randomization as reported by the subject in the eDiary.

17. Minimum 70% compliance with the eDiary assessment schedule.

    - For example, 10 out of the 14 days between each visit in the run-in/optimization periods, prior to randomization as reported by the subject in the eDiary.

3.2 Exclusion criteria

Subjects must not enter the study if any of the following exclusion criteria are fulfilled:

1. Clinically important pulmonary disease other than asthma (eg, active lung infection, COPD, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation

syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).

2. Any disorder, including but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that is either not stable or could in the opinion of the Investigator:

    - Affect the safety of the subject throughout the study
    - Influence the findings of the studies or their interpretations
    - Impede the subject's ability to complete the entire duration of study

3. Known history of allergy or reaction to any component of the IP formulation.

4. History of anaphylaxis following any biologic therapy.

5. A helminth parasitic infection diagnosed within 6 months prior to the date informed consent or assent obtained that has not been treated with, or has failed to respond to, standard of care therapy.

6. History of clinically significant infection, including acute upper or lower respiratory infections, requiring antibiotics or antiviral medication within 30 days prior to the date informed consent or assent is obtained or during the run-in period.

7. Tuberculosis requiring treatment within the 12 months prior to enrolment (Visit 1).

8. Any clinically significant abnormal findings in physical examination, vital signs, dECG, haematology, clinical chemistry, or urinalysis during the run-in period, which in the opinion of the Investigator, may put the subject at risk because of his/her participation in the study, or may influence the results of the study, or the subject's ability to complete entire duration of the study.

9. History of chronic alcohol or drug abuse within 12 months of the enrolment visit (Visit 1), or a condition associated with poor compliance as judged by the Investigator.

10. Positive hepatitis B surface antigen or hepatitis C virus antibody serology. Subjects with a history of hepatitis B vaccination without a history of hepatitis B are allowed to be enrolled.

11. History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at enrolment (Visit 1), or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report.

12. Current tobacco smoking (smoking must have stopped for ≥ 3 months prior to enrolment (Visit 1)) or a history of tobacco smoking for ≥ 10 pack-years (one pack year = 20 cigarettes smoked per day for 1 year).

13. History of cancer with the exception of:

    - Subjects who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix provided that the subject is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained.

    - Subjects who have had other malignancies provided that the subject is in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained.

14. Use of immunosuppressive medication (including but not limited to: methotrexate, troleandomycin, cyclosporine, azathioprine, and intramuscular long-acting depo corticosteroids) within 3 months prior to the date informed consent or assent is obtained. Chronic maintenance OCS for the treatment of asthma is allowed.

15. Clinically significant asthma exacerbation, in the opinion of the Investigator, including those requiring use of systemic corticosteroids or increase in the maintenance dose of OCS within 30 days prior to the date of informed consent or during the enrolment/run-in or last 2 weeks of optimization period.

16. Asthma control reached at an OCS dose of ≤5 mg during the run-in/OCS optimization period (Visit 2 to Visit 6, for subjects undergoing dose optimization)

17. Qualifies for 3 consecutive dose reductions at Visits 2-4 and continues to meet OCS dose reduction criteria at Visit 5 (for subjects undergoing dose optimization).

18. Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent or assent is obtained.

19. Receipt of any marketed or investigational biologic agent (eg. omalizumab) within 4 months or 5 half-lives prior to the date of randomization, whichever is longer.

20. Receipt of live attenuated vaccines within 30 days prior to the date of randomization and during the treatment and the follow-up period.

- Receipt of inactive/killed vaccinations (eg, inactive influenza) are allowed, provided they are not administered within 5 days before/after any study visit.

21. Receipt of any investigational non-biologic agent within 30 days or 5 half lives prior to informed consent or assent being obtained, whichever is longer.

22. Previous receipt of tralokinumab (CAT-354).

23. Initiation of new allergen immunotherapy or change in existing immunotherapy is not allowed within 30 days prior to the date of informed consent. However, allergen immunotherapy initiated prior to this period may be continued provided there is a span of at least 5 days between the immunotherapy and IP administration.

24. Current use of any oral or ophthalmic non-selective β-adrenergic antagonist (eg, propranolol).

25. Current use of five-lipoxygenase inhibitors (eg, Zileuton) or roflumilast.

26. Subjects who have undergone bronchial thermoplasty.

27. Major surgery within 8 weeks prior to the enrolment Visit 1, or planned in-patient surgery or hospitalization during the study period.

28. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥ 2.5 times the upper limit of normal (ULN) at enrolment (Visit 1).

29. Pregnant, currently breast-feeding, or lactating women.

30. Previous randomization in the present study.

31. Concurrent enrolment in another clinical study where the subject is receiving an IP.

32. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

33. Employees of the clinical study site or any other individuals directly involved with the planning or conduct of the study, or immediate family members of such individuals.

34. Individuals who are legally institutionalized.

For procedures for withdrawal of incorrectly enrolled subjects see Section 3.4.

3.3 Subject enrolment and randomization

Investigator(s) should keep a record (ie, a subject screening log) of subjects who have been pre-screened/screened. The pre-screening/screening log will be evaluated periodically by AstraZeneca and/or its delegates during routine monitoring visits.

The Investigator(s) will:

1. Obtain signed informed consent or assent from the potential subject, or their guardian/legal representative, before any study specific procedures are performed.

2. Assign the potential subject a unique enrolment number (which begins with an 'E') via the Interactive Web Response System/ Interactive Voice Response System (IWRS/IVRS) at Visit 1.

3. Determine subject eligibility. See Section 3.1and 3.2.

4. Assign the eligible subject unique randomization code IWRS/IVRS at Visit 6.

Subjects will be allocated to receive tralokinumab or placebo in a 1:1 ratio (ie 60 subjects on tralokinumab versus 60 subjects on placebo). Randomization numbers will be grouped in blocks. Randomized subjects who discontinue will not be replaced. If a subject withdraws from participation in the study, then his/her enrolment/ randomization code cannot be reused.

Specific information concerning the use of the IWRS/IVRS will be provided in a separate instruction manual.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be randomized or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the subject from treatment, with a consideration whether or not there is a safety concern. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Randomization codes will be assigned strictly sequentially in each stratum as subjects become eligible for randomization.

The randomization code will be assigned from a randomization list prepared by an internal AstraZeneca computerized system (Grand). All subjects will be stratified at randomization by age group (adults versus adolescents). Adult subjects will also be stratified at randomization by the baseline oral corticosteroid dose (≤ 10 mg versus > 10 mg prednisone or prednisolone).

3.6 Methods for ensuring blinding

This is a double-blind study in which tralokinumab and placebo are visually distinct from each other. Neither the subject nor any of the Investigator or sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the subjects will be aware of the treatment received. Since tralokinumab and placebo are visually distinct, IP will be handled by an unblinded IP manager at the site and will be administered by an unblinded investigational site study team member who will not be involved in the management of study subjects (this could be the same person).

Should an issue arise with the IP (e.g. damaged kit or syringe) that has been assigned to a subject prior to administration, or any other unexpected event with the kit or syringe (e.g. a malfunction during IP administration) the unblinded IP manager at the site will contact a predetermined unblinded AstraZeneca site monitor (who is not otherwise involved in the project) to determine whether any specific actions are required.

A blinded AstraZeneca site monitor will perform IP accountability. In the event that the treatment allocation for a subject becomes known to the Investigator or other study staff involved in the management of study subjects, or needs to be known to treat an individual subject for an AE, the sponsor must be notified *immediately* by the Investigator and if possible, before unblinding.

All packaging and labelling of IP will be done in such way as to ensure blinding for all sponsor and investigational site staff (other than the unblinded IP manager who will directly handle the pre-filled syringes).

The following personnel will have access to the randomization list:

- IVRS/IWRS Vendor

- those generating the randomization list

The information in the randomization list will be kept from other personnel involved in the conduct of the study, and in a secure location until the end of the study.

No member of the extended study team at AstraZeneca, or any CRO handling data, will have access to the randomization scheme during the conduct of the study, with the exception of the Supply Chain Study Management department and the Patient Safety department at AstraZeneca and personnel at the bioanalytical lab performing the PK sample analysis.

A DSMB will review the safety data and will assess the safety of the interventions for adolescents. The DSMB will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing (see Section 6.8.1), if and as required. The personnel involved in the clinical study at AstraZeneca will remain blinded to these analyses and will have no knowledge of the results presented to the DSMB.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) or pharmacists at the study sites from the IVRS/IWRS. The instructions for unblinding will be described in the IVRS/IWRS user manual that will be provided to each site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

3.8 Restrictions during and after the study

Fertile and sexually active female subjects (including adolescent females) should use highly effective contraceptive methods throughout the study and at least for 16 weeks (5 half-lives) after last administration of the IP.

Subjects must abstain from donating blood or plasma from the time of informed consent or assent and up to 16 weeks (5 half-lives) after last dose of IP.

3.9 Discontinuation of investigational product

At any time, subjects are free to discontinue IP or withdraw from the study (ie, IP and assessments – see Section 3.10), without prejudice to further treatment. A subject that decides to discontinue the IP will always be asked about the reason(s) for their decision to withdraw and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (as described in Section 6). The enrolment/randomization code of the withdrawn subject cannot be reused.

3.9.1 Procedures for discontinuation of a subject from investigational product

Subjects will be discontinued from IP in the following situations:

1. Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment

2. The subject experiences an AE that, in the opinion of the Investigator, contraindicates further dosing

3. The development of any risk to the subject as judged by the Investigator or AstraZeneca

4. Severe non-compliance with the study protocol

5. Pregnancy

6. Lost to follow-up[1]

7. Development of any study specific criteria for discontinuation, including:

    a) An anaphylactic reaction to the IP requiring administration of epinephrine

    b) A helminth parasitic infestation requiring hospitalization

    c) An asthma-related event requiring intubation

    d) Any malignancy

8. Development of one or more of the following:

    a) Confirmed ALT or AST increase of ≥8 x ULN

    b) Confirmed ALT or AST increase of ≥5 x ULN for more than 2 weeks

    c) Confirmed ALT or AST increase of ≥3 x ULN and total bilirubin of ≥2 x ULN

    d) ALT or AST of ≥3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (≥5%)

Subjects who discontinue IP or the study will always be asked about the reason(s) for discontinuation and the presence of any AEs. The Principal Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. They will also immediately inform AstraZeneca of the withdrawal. Adverse events will be followed up (see Section 6) and any questionnaires (eg, for patient reported outcomes) are to be completed.

Discontinuation of IP does not necessarily mean discontinuation of follow-up or termination of study participation. Compliant subjects who are discontinued from the IP should be

[1] A subject is considered lost to follow up when any of the following attempts of contact are failed: at least 3 attempts of either phone calls, faxes or emails; having sent 1 registered letter/certified mail; or one unsuccessful effort to check the status of the subject using publicly available sources, if allowed by local regulations.

encouraged to continue to undergo all study related visits/procedures for the full 40 -week study period in order to support the final efficacy and safety analysis for tralokinumab (see section 8). The reason for premature discontinuation of IP will be documented in the source documentation and recorded in the electronic case report form (eCRF).

It is essential to collect as much data as possible for all subjects throughout the study and especially all potential endpoint data. Complete withdrawal from the study (ie, withdrawal of consent) has a direct negative impact on the potential validity of all study data and should be avoided wherever possible.

Subjects who prematurely discontinue IP should return to the study site and complete procedures described for the IP Discontinuation (IPD) visit (see Table 2).

At the IPD visit, the subject will be given three options as to how they will be followed up as follows:

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 (such as OCS dose), and asthma exacerbation information. For option 1, all procedures will be done at each visit as indicated in Table 2.

The subject's decision needs to be documented in the eCRF and the specific section in the ICF/assent form addendum needs to be signed by the subject.

Should the subject choose option 3 above, they will complete the IPD visit immediately and then a follow up telephone call at week 40. If the subject chooses either option 1 or 2, they will complete the IP Discontinuation visit immediately and then the EOT visit at week 40. The EOT visit will be completed immediately in the case of early withdrawal from option 1 or 2.

Subjects who initially chose options 1 or 2 and subsequently cannot or do not wish to comply with the requirements of the chosen option, can choose to continue with a less invasive option

(ie: Subject initially choosing option 1 can continue with 2 or 3, subjects initially choosing option 2 can continue with 3).

Subjects who do not wish to have any follow up contact at all, will be discontinued from the study. All discontinued subjects must return the electronic patient reported outcome (ePRO) and electronic PEF devices at the EOT visit.

Completion, or early termination of IP treatment, will be registered via the IWRS/IVRS for each subject.

For subjects who wish to withdraw from the study completely, refer to Section 3.10.2.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screen failures are subjects who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These subjects should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (ie, subject does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures, and not randomized subjects.

3.10.2 Withdrawal of the informed consent or assent

Subjects are free to withdraw from the study at any time (ie, from receiving IP and/or having assessments performed), without prejudice to further treatment.

A subject who withdraws their consent or assent will always be asked about the reason(s) for their decision to withdrawal, and the presence of any AE. The Investigator will follow up AEs outside of the clinical study. The subject must return the ePRO and ePEF devices.

If a subject withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

If the subject only withdraws consent for the retention of blood samples for future exploratory use (eg, study of markers of asthma, identifying potential new drug targets for asthma, or for assay development purposes), the subject will not be withdrawn from the study.

Withdrawal of consent from the study must be ascertained and documented by the Investigator and recorded in the eCRF as well as in the Informed Consent Form (ICF) or assent form. The ICF or assent form must be re-signed and dated by both the subject and the Investigator.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan – Enrolment/Run-in/OCS optimization period

***subjects with a documented failure of OCS reduction within 6 months prior to Visit 1 do not need to enter the 8 week OCS optimization period**

Assessment/ activity	Enrolment/ Run-in	OCS optimization period			
	V1[a]	V2	V3	V4	V5
	(w–10)	(w–8)	(w–6)	(w–4)	(w–2)
	Visit window (days)				
	N/A	±3	±3	±3	–3
Informed consent	X				
Inclusion/exclusion criteria	X	X	X	X	X
Demographics	X				
Medical/Surgical and asthma history	X				
Complete physical examination	X				
Brief physical examination		X	X	X	X
Weight, Height	X				
Vital Signs	X	X	X	X	X

Assessment/ activity	Enrolment/ Run-in	OCS optimization period			
	V1[a]	V2	V3	V4	V5
	(w–10)	(w–8)	(w–6)	(w–4)	(w–2)
	Visit window (days)				
	N/A	±3	±3	±3	–3
dECG	X				
Serum chemistry	X				
Haematology	X				
Serum Biomarkers	X				
FE_{NO}	X				
Urinalysis (dipstick)	X				
Serology (hepatitis B,C; HIV-1; HIV-2)	X				
Serum pregnancy test	X				
FSH[b]	X				
Dispense PEF meter and eDiary	X				
PEF adherence check		X	X	X	X
Asthma Daily Diary adherence check		X	X	X	X
ACQ-6 at the site	X				
ACQ-6 adherence check		X	X	X	X
AQLQ (S) +12 at the site	X				

Assessment/ activity	Enrolment/ Run-in	OCS optimization period			
	V1[a]	V2	V3	V4	V5
	(w–10)	(w–8)	(w–6)	(w–4)	(w–2)
	Visit window (days)				
	N/A	±3	±3	±3	–3
AQLQ (S) +12 adherence check		X	X	X	X
Healthcare resource utilization	X				
Pre-BD spirometry	X	X	X	X	X
Run in reversibility (Post-BD spirometry) [c]	X	X			
Assessment of asthma exacerbations		X	X	X	X
OCS switch to prednisone or prednisolone if required	X				
OCS dose reduction		X[e]	X	X	
OCS dose increase, if indicated [d]					X
Adverse events	X	X	X	X	X
Concomitant medication	X	X	X	X	X

a Visit 1 can be performed over a period of 3-working days, with the exception of documentation of informed consent and assent (if applicable), which can be completed up to 30 days prior to Visit 1. For subjects not undergoing dose optimization (Visit 2-Visit 5), the next visit after Visit 1, will be Visit 6 (to be scheduled 14 up to 17 days after Visit 1).

b FSH test done only for female subjects to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 month

c If there is no evidence of documented reversibility within 6 months prior to Visit 1, the reversibility criterion must be met at Visit 1 or Visit 2 or Visit 6 (for subjects not required to undergo dose optimization). For reversibility assessment at Visit 1 (and Visit 2 or 6, if required) the full procedure as defined in section 5.1.4.1 should be

followed until the subject either meets FEV1 reversibility requirement (≥12% and ≥200 mL) or completes all steps. For patients with historical reversibility or once the reversibility criterion is met, only step 1 of the reversibility assessment (5.1.4.1) is required.
The Visit 2 reversibility assessment (Post-BD spirometry) will only be performed if the run-in reversibility criterion is not met at Visit 1 or if there is no documented history of reversibility.

d If the subject fails to meet titration criteria at Visits 3-4, the OCS dose should be returned to one level higher and Visit 5 should be activated on the same day

e Visit where OCS dose titration will not be based on the protocol captured set of baseline data and details are included in Section 4.1.2

Table 2 Study plan – Treatment and follow-up period

Assessment/ activity	Induction phase						Reduction Phase										Maintenance Phase				EOT	FU	FU	IPD	UNS[g]
	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28		
	(W 0)	(W2)	(W4)	(W 6)	(W8)	(W10)	(W 12)	(W 14)	(W16)	(W18)	(W 20)	(W 22)	(W24)	(W26)	(W 28)	(W30)	(W32)	(W 34)	(W 36)	(W 38)	(W 40)	(W 44)	(W 54)		
	Visit window[a] (days)																								
	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	**N/A**	**N/A**
Inclusion/ exclusion criteria	X																								
Complete physical examination	X																				X			X	X

Assessment/ activity	Induction phase						Reduction Phase										Maintenance Phase				EOT	FU	FU	IPD	UNS[g]
	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28		
	(W 0)	(W2)	(W4)	(W 6)	(W8)	(W10)	(W 12)	(W 14)	(W16)	(W18)	(W 20)	(W 22)	(W24)	(W26)	(W 28)	(W30)	(W32)	(W 34)	(W 36)	(W 38)	(W 40)	(W 44)	(W 54)		
	Visit window[a] (days)																								
	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	**N/A**	**N/A**
Brief physical examination		X	X	X	X	X	X		X		X		X		X		X		X			X			
Weight	X																				X			X	
Height																					X[h]			X[h]	
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X
dECG	X																				X			X	
Serum chemistry	X						X										X				X			X	X
Haematology	X	X	X		X		X		X		X		X		X		X		X		X	X	X	X	X
Urinalysis (dipstick)	X						X										X				X			X	
Urine pregnancy test (dipstick)[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Total IgE	X																				X			X	
Phadiatop	X																								

Assessment/ activity	Induction phase						Reduction Phase										Maintenance Phase				EOT	FU	FU	IPD	UNS[g]
	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28		
	(W 0)	(W2)	(W4)	(W 6)	(W8)	(W10)	(W 12)	(W 14)	(W16)	(W18)	(W 20)	(W 22)	(W24)	(W26)	(W 28)	(W30)	(W32)	(W 34)	(W 36)	(W 38)	(W 40)	(W 44)	(W 54)		
	Visit window[a] (days)																								
	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	**N/A**	**N/A**
FE_{NO}	X						X						X				X				X			X	
PK	X	X											X								X	X	X	X	
ADA/nAB	X												X									X	X		
Serum biomarkers	X		X		X		X										X				X	X		X	
PEF adherence check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Asthma Daily Diary adherence check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
ACQ-6 at the site[d]	X																				X			X	
ACQ-6 adherence check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
AQLQ (S) +12 , WPAI+CIQ, EQ-5D-5L at the site[e]	X																				X			X	

Assessment/ activity	Induction phase						Reduction Phase										Maintenance Phase				EOT	FU	FU	IPD	UNS[g]
	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28		
	(W 0)	(W2)	(W4)	(W 6)	(W8)	(W10)	(W 12)	(W 14)	(W16)	(W18)	(W 20)	(W 22)	(W24)	(W26)	(W 28)	(W30)	(W32)	(W 34)	(W 36)	(W 38)	(W 40)	(W 44)	(W 54)		
	Visit window[a] (days)																								
	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	**N/A**	**N/A**
AQLQ (S) +12, WPAI+CIQ, EQ-5D-5L adherence check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Assessment of asthma exacerbations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X
OCS dose titration							X		X		X		X		X										X[i]
Pre-BD spirometry[k]	X						X		X		X		X		X		X				X	X		X	X
Post-BD spirometry[j]	X						X														X			X	
Health care resource utilization	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	

Assessment/ activity	Induction phase						Reduction Phase										Maintenance Phase				EOT	FU	FU	IPD	UNS[g]
	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28		
	(W 0)	(W2)	(W4)	(W 6)	(W8)	(W10)	(W 12)	(W 14)	(W16)	(W18)	(W 20)	(W 22)	(W24)	(W26)	(W 28)	(W30)	(W32)	(W 34)	(W 36)	(W 38)	(W 40)	(W 44)	(W 54)		
	Visit window[a] (days)																								
	0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	**N/A**	**N/A**
Randomization	X																								
Administration of IP[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a All visits are to be scheduled from the date of randomization but not from the date of previous visit
b Vital signs will be taken pre-dose prior to administration of IP. Subjects will be observed 2 hours post treatment for Visits 6, 7, 8 and 9. For all other visits where IP is administered, subjects will be observed for a minimum of 1 hour.
c For WOCBP and adolescent females, urine pregnancy test (dipstick) to be done at centre at each treatment visit prior to IP administration.
d ACQ-6 performed at the site unless completed at home the day prior.
e ePROs performed at the site unless completed at home the day prior.
f In case of anaphylaxis additional samples will be taken (see Section 6.7)
g Unscheduled visits may be initiated as needed, and additional assessments performed at these visits. At unscheduled visits for assessing an asthma exacerbation, at a minimum, these assessments need to be performed. Other unscheduled visits may be initiated as needed, and assessments performed as per investigator's judgement.
h Height will be measured for adolescent subjects only.

i Uptitration only

j On Visit 6 (if reversibility criterion has already been met at Visit 1 or Visit 2 or for patients with historical reversibility), Visit 12, Visit 26 and IPD Visit: Only step 1 of the reversibility assessment (Section 5.1.4.1) is required.

k The investigator can consider to perform a pre-BD spirometry assessment at visits where this is not required.

4.1 Enrolment and run-in/optimization period

4.1.1 Run-in period (Visit 1 – Visit 2)

Each potential subject who is at, or over the age of majority (as per local law) will provide informed consent prior to the start of any study specific procedures and undergo assessments applicable for this visit (see Table 1).

For subjects less than the age of majority, in addition to the subject providing informed assent, the subject's legal guardian must also provide their informed consent.

With the exception of documentation of informed consent and assent (if applicable), which can be completed up to 30 days prior to Visit 1, all other Visit 1 procedures should be completed within a 1 to 3-working day window. The 3-day window is to enable subjects to return if necessary for the spirometry assessments on a day when they have had their bronchodilator medications withheld in accordance with the spirometry instructions (see section 5.1.4). The registration of the subject's enrollment via IWRS/IVRS should occur on the day when the subject's Visit 1 procedures are performed.

Visit 1 assessments are primarily concerned with assessing the subject's eligibility (inclusion/exclusion) criteria, including their asthma disease state, the requisite level of severity based on maintenance medications and exacerbation history. The baseline for the ePRO parameters (OCS optimization period) will be established from Visit 1 to Visit 2.

Spirometry will also be performed at Visit 1. Subjects must have a pre-BD FEV_1 value <80% of their PNV (<90% for subjects 12 to 17 years of age). Should this criterion not be met or cannot be performed at Visit 1, subjects must fulfill it at Visit 2 or Visit 6 (if a subject is not required to undergo dose optimization) in order to proceed in the study (as per Section 3.1, criterion 9). If not, the subject will be screen failed.

Subjects must have a post-BD reversibility in FEV_1 of ≥12% and ≥200 mL at enrolment (Visit 1) or documented reversibility within 6 months prior to Visit 1 with available source documentation. The use of the historical reversibility to meet this criterion must be reviewed with the sponsor study physician prior to the run-in/optimization period. If there is no evidence of documented reversibility within 6 months prior to Visit 1 or this criterion is not met at Visit 1, the criterion must be met at Visit 2 or Visit 6 (if subject is not required to undergo dose optimization), see section 5.1.4.1. Visit 2 post-BD spirometry will only be performed if the run-in reversibility criterion is not met at Visit 1 or if there is no documented history of reversibility.

Other study assessments and procedures to be performed at this visit include the recording of the subject's demographics, a complete physical examination (including height and weight), vital signs, a dECG, medical/surgical history and concomitant medications, collection of blood samples for haematology/clinical chemistry, serology, collection of a urine sample for dipstick and urinalysis (if applicable), and a pregnancy test for WOCBP.

A record of physician-diagnosed asthma, ICS/LABA use, use of other asthma controllers is required source documentation. A subject's verbal history suggestive of asthma, but without supporting documentation is not sufficient to satisfy inclusion criteria 5 and 6.

Current, regular use of an ICS and LABA for at least 3 months prior to enrolment (Visit 1) and OCS use for at least 6 continuous months prior to enrolment (Visit 1) must be documented in the source.

The ICS and LABA may have been administered as either a fixed dose or as 2 separate inhalers, and consistent with dose limits set by inclusion criterion 6. Stable dose of OCS must have been maintained for at least 1 month prior to Visit 1. This documentation may be in the form of a recent, active medication list as per a healthcare professional(HCP) note, or filled prescription.

Subjects with documented failure of OCS reduction

Subjects with documented failure of OCS reduction within 6 months prior to Visit 1 do not need to enter the 8 week optimization period. These subjects will complete the 2 week run-in period prior to randomization (after discussion with the study sponsor physician) and proceed directly to Visit 6. Failed attempts at OCS dose reduction are those, which resulted in documented clinical deterioration or reduced lung function attributed to asthma, demonstrated by documented occurrence of at least one of the following:

- Pre-BD FEV_1 < 80% of personal baseline
- Morning PEF < 80% of personal baseline
- Night time awakenings increase of > 50% of mean personal baseline
- Rescue medication use, for example salbutamol > 4 puffs/day above mean personal baseline
- Requirement for an OCS burst (large temporary increase) to treat an asthma exacerbation provoked by steroid reduction

After confirmation of initial entry criteria the subject will be supplied with an electronic handheld spirometer (peak flow meter) to monitor home lung function, and an ePRO device to record asthma symptoms and complete relevant questionnaires (see Section 5.2.2 for further details).

Subjects will continue on their current ICS/LABA and other maintenance asthma controller medications (if applicable) with no changes.

At the enrolment visit, subjects who are not currently using prednisone or prednisolone as their maintenance corticosteroid will be switched to the corresponding prednisone/prednisolone equivalent dose given as a daily dose.

4.1.2 OCS Optimization period (Visit 2 – Visit 5)

For those subjects who have not had a documented failure at OCS reduction, they will enter an OCS optimization period that will be a maximum of 8 weeks in duration (from Visit 2, Week -8 to Visit 6, Week 0).

The subjects should remain on their current ICS/LABA treatment and other maintenance asthma controller medications (if applicable) with no changes throughout this period. Assessments applicable for the period are listed in Table 1.

During the OCS optimization period, a subject's OCS dose will be titrated down (see Section 5.1.2) to ensure the subject is taking the minimum effective OCS dose without losing asthma control.

The OCS dose titration must be initiated at Visit 2. The Investigator should follow the titration schedule listed in Table 3. Visit 2 is the only titration visit that will not be based upon a protocol-captured set of baseline data, because the first baseline data capture period is not yet complete. Visit 2 spirometry and data captured in the electronic diary compared with a historic baseline from the past 6 months can be used for the Investigators who would want to initiate the titration at this visit. Subjects who are judged not to be candidates for OCS dose reduction at Visit 2, based upon asthma symptoms or other clinical reasons in the opinion of the Investigator, should be screen-failed.

From Visit 3 onwards, the dose of the OCS may be reduced only if all criteria listed in Section 5.1.2 are met. The reductions can occur at 2-week intervals according to the titration schedule (see Table 3). The optimized dose of OCS is defined as a lowest dose of OCS at which the subject meets criteria listed in section 5.1.2. In cases when the subject is optimized on their OCS dose prior to Visit 5 (Week-2), he/she should be maintained at the optimized dose of OCS for at least 2 weeks and then can be randomized. If the subject fails to meet the OCS dose titration criteria at Visits 3-4, the OCS dose should be returned to one level higher and Visit 5 should be activated on the same day. The optimized dose reached during the OCS optimization period becomes the subject's baseline OCS dose for analysis purposes.

If a subject does not meet the down titration criteria, the OCS dose should be returned to the previous effective dose (i.e., the higher dose level prior to the titration criterion not being met), which will be considered the minimal effective dose and should be maintained on that OCS dose until randomization (Visit 6).

If a subject experiences an asthma exacerbation during this period, a temporary increase of systemic steroids (bolus/burst dosing) will be performed; when clinically indicated, the systemic corticosteroid dose used in the burst will be tapered down over 7 to 10 days to a dose above the pre-burst dose. That is the subject should be placed on an OCS dose one step higher

(or two in the judgement of the investigator) than the dose they were on when the exacerbation occurred. In that instance the subject must maintain the optimal dose for the protocol required 2 weeks prior to randomization.

Subjects who are considered by Investigators not to be candidates for OCS dose reduction, based upon asthma symptoms or other clinical reasons should be screen-failed.

If a subject reaches asthma control at an OCS dose of ≤5 mg during this phase, the subject will be a screen failure and will not be randomized.

If the subject does not reach the optimized dose of the OCS by the end of the run-in/optimization period the subject should be screen failed and cannot be randomized.

Subjects whose compliance with the electronic diary is <70% will be given the option, one time during screening, to reschedule a study visit (with the exception of Visit 6) within 72 hours.

4.1.3 Re-screening

Subjects who experience an asthma exacerbation within 30 days prior to ICF date, during the run-in period or optimization period whereby a subject has not maintained the optimal dose for the protocol required 2 weeks prior to randomization should be screen failed (the optimization period will not be extended). They may be re-screened no sooner than 30 days after their last dose of systemic steroids.

Subjects with respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the screening/run-in period may also be re-screened.

If the reason for screen failure was transient (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits), subjects may potentially be re-screened. These cases should be discussed with the AstraZeneca Study Physician and documented approval for re-screening should be filed in the Investigator Study File (ISF).

Any re-screened subject will be re-enrolled and reassigned their originally assigned enrolment number after signing a new Informed Consent Form (ICF), or assent form, and after all Visit 1 assessments have been performed as listed in Table 1 (with the exception of testing for HIV1 and HIV2, hepatitis B and C, and FSH).

Re-enrolment is only allowed once for any subject.

Re-screening of a subject for any other reason will be allowed only upon approval of the AstraZeneca Study Physician. A documented approval for re-screening should be filed in the Investigator Study File (ISF).

4.2 Randomized treatment period (Visit 6 – Visit 26)

The randomized treatment period is divided into 3 phases: induction phase (Section 4.2.1), reduction phase (Section 4.2.2), and maintenance phase (Section 4.2.3).

Inclusion criteria at randomization will be confirmed at Visit 6. Before randomization the subject's compliance with usual asthma medications, OCS, and ePRO completion must be confirmed (see Section 3.1 , inclusion criteria 14, 16, 17).

Subjects confirmed to be eligible will be randomized in a 1:1 ratio to receive either tralokinumab 300 mg or placebo every two weeks throughout the treatment period. The first dose of the IP will be administered at Visit 6 after the subject's randomization via IVRS/IWRS.

Following randomization the subject will receive double-blind treatment for 40 weeks, with the last dose of tralokinumab /placebo administered at Visit 25 (Week 38).

If worsening of symptoms occurs, the OCS dose may be increased to the next dose increment. If a subject experiences an asthma exacerbation, a temporary increase of systemic steroids (bolus/burst dosing) will be performed; when clinically indicated, the systemic corticosteroid dose used in the burst will be tapered down over 7 to 10 days to a dose above the pre-burst dose.

4.2.1 Induction Phase

The induction phase will start at Week 0 (Visit 6) and will continue through Week 12 (Visit 12) in which subjects will remain on all of their regular asthma controller medications. Subjects will continue with the OCS dose that was achieved during OCS optimization unless an exacerbation occurs.

4.2.2 Reduction Phase

The OCS reduction period will start at week 12 (Visit 12) and will be completed at Week 32 (Visit 22). The first reduction of the OCS dose should occur at the Week 12 (Visit 12). The OCS reduction at Visit 12 is the only down-titration during the reduction phase that will not be based upon a protocol-captured set of baseline data. Subsequent OCS dose reductions can occur at 4-week intervals according to the titration schedule of OCS dose reductions presented in Table 4. These subsequent OCS reductions will only take place if all criteria listed in Section 5.1.2 are met. The presence of an asthma exacerbation, changes in symptoms, and rescue medication use will be assessed. Subjects who experience an asthma exacerbation requiring evaluation in an urgent care centre, in ED, hospitalization, or temporary increase of systemic steroids (bolus/burst dosing), in the judgment of the Investigator should be returned to the previous effective OCS dose (i.e., the higher dose level prior to the titration criterion not being met) after they have returned to their baseline level of asthma control that is established prior to the randomization visit. Further dose reductions can be considered in the opinion of the PI (further reductions will follow the scheduled titration, see Table 4).

Note: OCS dose reduction may take place only when criteria for OCS dose reduction are met (not applicable for Visit 12; see section 5.1.2).

4.2.3 Maintenance Phase

The maintenance phase is 8 weeks after Week 32 (Visit 22). During this phase, subjects should be maintained on the stable dose of OCS achieved during the reduction phase unless an exacerbation occurs. If the requirement for OCS was eliminated then the subject will be maintained without any OCS.

4.3 Follow-up period

Subjects will have follow-up visits at Weeks 44 and 54 respectively. Subjects will be requested to return to the study centre for the follow-up assessments. During these visits subjects will be assessed for any ongoing safety issues and any potential prospective AEs, serum biomarker, PK and immunogenicity samples will be collected (see Table 2).

5. STUDY ASSESSMENTS

The Rave® Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data is recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigator will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site upon completion of the study.

5.1 Efficacy assessments

5.1.1 Assessment of OCS dose

During the run-in/OCS optimization period the minimum OCS dose while not losing asthma control will be reached for subjects that have undergone dose optimization. The optimized dose will be considered as the baseline OCS dose.

The baseline dose will be the dose at randomization, regardless of whether or not the subject has undergone dose optimization.

The baseline OCS dose should be maintained at the same level from Visit 6 up to Visit 12 (induction phase).

If the dose reduction criteria are met (see Section 5.1.2), the dose reduction of the OCS will commence at Visit 12 and will continue at 4-weekly intervals until Visit 22 in accordance with the OCS dose titration schedule provided in Table 4 (reduction phase). During the reduction

phase a minimum stable OCS dose, or complete elimination of requirement for OCS, while maintaining asthma control, will be reached for each subject.

If a subject does not meet the titration criteria, the OCS dose should be returned to the previous effective dose (i.e., the higher dose level prior to the titration criterion not being met) and should be maintained on that OCS dose until EOT (Visit 26).

No adjustments should be made to the OCS dose after Visit 22 (the subject will enter the maintenance period).

The OCS dose changes will be documented in the source documentation and recorded in the appropriate eCRF form.

Subjects should complete the Asthma Daily Diary twice daily for at least 70% of the days before Visit 6 and the OCS reduction phase (Visit 12 to Visit 22) based on the Asthma Daily Diary for OCS dose titration. If the compliance falls under 70% during the treatment period (Visit 6 – Visit 22), OCS dose reduction may still be performed at the Investigator's discretion according to the protocol-specified titration criteria.

5.1.2 OCS dose titration

The OCS dose titration will follow the same approach for those subjects who have not had a documented failure at OCS reduction and enter the optimization phase (Visit 2 to Visit 6) and all subjects following the induction phase (Visit 12 to Visit 20).

For those entering the OCS dose optimization period, dose titration begins at Visit 2 (see Section 4.1.2).

For the optimization period, the baseline will be the mean of measures (morning PEFs, SABA use, night time awakenings, and total asthma symptom score) collected on each day between Visit 1 and Visit 2.

The dose titration during the treatment period will begin at Visit 12 and ends at Visit 20. Dose reduction begins at Visit 12 and it is the only titration visit during reduction phase that will not be based upon a protocol-captured set of baseline data. For all subjects entering the dose reduction phase, the baseline values will be the mean of measures (morning PEFs, SABA use, night time awakenings, and total asthma symptom score) collected on each day of the last two weeks prior to randomization regardless of whether they went through the OCS optimization period or not. For FEV_1, all efficacy assessments are relative to the pre-dose baseline obtained at randomization (Visit 6).

Subjects who meet all of the following criteria are eligible for OCS dose titration (dose reduction):

– Pre-BD $FEV_1 \geq 80\%$ of baseline FEV_1 at the clinic visit

- Mean of the morning PEF measures during 14 days prior to visit ≥ 80% of baseline mean morning PEF measure

- Not more than or equal to 50% increase compared to baseline in the proportion of nights with awakenings in the 14 days period prior to the 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 visit

- No asthma exacerbation requiring a burst of systemic corticosteroids since the previous visit

- Investigator judges subject's asthma control to be sufficient to allow OCS dose reduction

When a subject doesn't meet the above criteria, further reduction of the OCS dose will be stopped for the duration of the study and the subject will be returned to the dose one level higher.

For subject safety those that started on a higher dose of OCS will not be allowed to reduce their OCS dose to 0 during the OCS reduction phase. This is to protect the subject from potentially experiencing adrenal crisis. Throughout the reduction phase subjects should be monitored for the signs and symptoms of adrenal insufficiency. A minimum maintenance OCS dose will be required for subjects whose dose at Visit 6 is 15 – 30 mg/day (see Table 4 for the minimum dose that can be reached).

If, in the opinion of the Investigator, additional OCS dose reductions are not clinically indicated (due to disease factors that may affect subject safety), titration may be stopped. The subject should be returned to a dose one level higher (unless a temporary bolus/burst of steroid is warranted). Further dose reductions can be considered in the opinion of the PI (further reductions will follow the scheduled titration, see Table 4).

The titration schedule of OCS dose reductions is presented in Table 3 and Table 4.

Table 3 OCS dose titration schedule during the optimization period (V2 – V4)

Regimen	Starting dose of OCS (mg/day) at each visit of optimization period	Reduction by [a]
Daily regimen	12.5-30	5.0
	7.5-10	2.5

[a] During the Run-in/optimization period the reductions should occur at 2-week intervals.

Table 4 OCS dose titration schedule recommended during the reduction phase (V12-V20) [a,b]

Optimized dose at V6 W0	Visit 12 W12	Visit 14 W16	Visit 16 W20	Visit 18 W24	Visit 20 W28
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

[a] – All doses expressed in mg/day

[b-] 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). A daily dose of 1.25 mg may be administered as 2.5 mg every other day.

5.1.3 Assessment of asthma exacerbations

The treatment, including changes in the OCS dose and duration and the use of additional, potentially emergent therapies is at the discretion of the treating physician. For the purpose of the study, an asthma exacerbation will be defined as a worsening of asthma that leads to any of the following:

- A temporary bolus/burst of systemic corticosteroids for at least 3 days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids
    - Discontinuation due to an exacerbation after Visit 6 is not mandatory. Subjects who experience an exacerbation during the run-in period should be screen failed and may be considered for re-screening. Those who experience an exacerbation after randomization may remain on the investigative product at the PI's discretion. After the bolus/burst is complete, in the judgment of the PI, the subject may be returned to the higher OCS dose than the dose that preceded their exacerbation. Further dose reductions can be considered in the opinion of the PI (further reductions will follow the scheduled titration, see Table 4).
    - Up titration of OCS dose during optimization to one level higher is not considered an exacerbation
- An emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care 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 ≥ 24 hours) due to asthma

Worsening of asthma is defined as new or increased symptoms and/or signs (examination or lung function) that can be either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (diary-driven).

For those subjects entering the optimization period, the baseline for OCS reduction will be the mean of measures collected each day between Visit 1 and Visit 2.

For the dose reduction phase, the baseline will be the mean of measures collected 14 days prior to Visit 6. For those entering the run-in period only the 14 days between Visits 1 and 6 will be used for baseline calculations. For those entering the run-in/optimization period the 14 day period between Visits 5 and 6 will be used for baseline calculations.

The ePRO device will be programmed to alert both the patient and study centre when certain pre-specified worsening thresholds are crossed including:

- Decrease in morning peak flow ≥20% on at least 2 consecutive days compared with baseline, and/or
- An increase in rescue medication use of 4 or more puffs, or use of one new or additional nebulized β2 agonist on at least 2 consecutive days compared with the average use during baseline, and/or
- An increase of 2 nocturnal awakenings due to asthma over a 7 day period compared with the average during baseline, and/or
- An increase in total asthma symptom score (the sum of day time [evening assessment] and night time [morning assessment] of at least 2 units above the baseline average or the highest possible score (daily score of 6), on at least 2 consecutive days

If an exacerbation event is not associated with deterioration in at least 1 of the pre-specified objective measurements, the Investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF. Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

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

The subject may remain in the study after an exacerbation and continue to receive IP if the Investigator judges that it is medically appropriate for the subject to do so.

Reasonable attempts should be made by the Investigator to bring the subject into the study centre for evaluation of a diary alert or subject initiated asthma worsening, particularly when it results in additional treatment being prescribed. Study centre evaluations for asthma worsening may occur as an unscheduled (UNS) visit or as part of an ordinary centre visit if the worsening happens to be coincident with a scheduled visit window. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study centres (eg, by the primary care HCP or at an ED/hospital) and details entered into the exacerbation eCRF (EXACA module) in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the appropriate module of the eCRF.

5.1.4 Spirometry

General requirements

Pulmonary function will be measured by spirometry at the study site using equipment provided by a central vendor. Spirometry will be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005).

The vendor providing central spirometry services will be responsible for assuring that the spirometer used by each site meets ATS/ERS recommendations, and that the study site personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate spirometry procedures manual.

Time of day for scheduled site visit spirometry

All post-randomization spirometry assessments should be performed within ± 1.5 hours of the time that the randomization spirometry was performed. For example, if the randomization spirometry was started at 8:00 AM, then all subsequent spirometry testing needs to be initiated between 6:30 AM and 9:30 AM.

Important! Subjects should be instructed not to use their maintenance twice daily LABA or ICS/LABA combination within 12 hours of the scheduled site visit spirometry, as this will affect the pre-BD FEV_1 value; they may be taken subsequently, at the site. For theophylline and once daily bronchodilators a 48 hour washout period is required. **For the same reason subjects should not use their rescue SABA medication within 6 hours scheduled spirometry.** This restriction is particularly critical for efficacy measures taken during the treatment period, but should also facilitate meeting the run-in FEV_1 and reversibility eligibility criteria.

Options for handling subjects who have inadvertently taken their asthma medication within the restricted window are described in section 7.7.2.

Spirometry technique

Subjects should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Subjects should avoid eating a large meal for at least 2 hours prior to spirometry measurements at the site. All spirometry manoeuvres (irrespective of whether to obtain values for FEV1, FVC, $FEF_{25-75\%)}$ should be performed with the subject seated in an upright position. If this is not comfortable for the subject, standing is permitted. The same position should be used by the subject for each forced expiratory manoeuvre from enrolment throughout the study. The head must not be tilted during manoeuvres and the thorax should be able to move freely; hence tight clothing should be loosened. A nose-clip should be used for the manoeuvre. Mouthpieces of the same dimension and shape should be used by the subject from enrolment throughout the study.

The Spirometry manoeuvre consist of three phases; The first is maximal inspiration, the second a ”blast” of exhalation (to obtain the FEV1 value) and the last continued complete exhalation to the end of test. The subject should inhale rapidly and completely from functional residual capacity. It is Important that the preceding inspiration is fast and any pause at full inspiration be minimal (i.e. only for 1–2 s). The subject should be prompted to ‘‘blast,’’ not just ‘‘blow,’’ and he/she should be encouraged to fully exhale until end of test criteria are met. If the patient feels ‘‘dizzy’’, the manoeuvre should be stopped, since syncope could follow due to prolonged interruption of venous return to the thorax. Manoeuvres that do not meet the end of test criteria should not be used to satisfy the requirement of three acceptable manoeuvres. However, early termination, by itself, is not a reason to eliminate all the results from such a manoeuvre from further consideration. Please note that Information such as the FEV1 may be useful (depending on the length of exhalation) and can be reported from these early terminated manoeuvres.

To allow recording of the FVC value it is important that the whole manouvre lasts for at least 6 seconds. Ensure that none of the following has occurred: coughing during the first second, glottis closure, leak or obstruction of the mouthpiece (by the tongue).

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each spirometry session. There should be at least 3 efforts that meet the ATS/ERS acceptability criteria with the highest value and second highest value for FEV1 and FVC meeting the ATS/ERS reproducibility criteria. The largest FVC and the largest FEV1 should be recorded after examining the data from all of the usable curves, even if they do not come from the same curve. If the criteria for acceptability and reproducibility are not met with the first 3 expiratory efforts, then additional attempts are required up to a maximum of 8. If the reproducibility criterion is not fulfilled after the maximum number of manoeuvres has been performed, the highest of the FEV1 and FVC value that is deemed acceptable should be selected.

The mean forced expiratory flow between 25% and 75% of the FVC ($FEF_{25–75\%}$) is taken from the blow with the largest sum of FEV1 and FVC. The $FEF_{25–75\%}$ must be measured with an accuracy of at least +5% of reading or +0.2 L whichever is greater. It is highly dependent on the validity of the FVC measurement and the level of expiratory effort.

The absolute measurement (for FEV_1), and the percentage of PNV (Quanjer et al 2012) will be recorded.

Order of administration of usual asthma controller medication and IP relative to scheduled pre-and post-BD spirograms.

On visits when spirometry is performed the subject´s usual asthma controller medication should be withheld until the whole procedure for spirometry has been completed; usual asthma controller may be given after final post-BD spirograms. IP dosing should also be withheld until pre-BD spirometry has been completed.

Record keeping

A signed and dated copy of the pre- and post- BD printout must be kept at the study site for source data verification. The printout must be marked with the study code, subject enrolment code, date and time of measurement, and visit number.

Spirometry references

The Global Lung Function Initiative (GLI) equations will be used to determine the subjects PNV values and are pre-programmed into the spirometer (Quanjer et al 2012).

FEV_1, expressed as percent of the PNV, will be calculated as follows:

$FEV_1\%$ of PNV = (FEV_1 measured/FEV_1PNV) x 100

5.1.4.1 Reversibility test and post-BD FEV_1 efficacy assessment

Complete the initial (pre-BD) FEV1 measurement (Section 5.1.4) before commencing the post-BD assessment.

It is important that the subject has withheld each of their theophylline and BD medications for the minimum period of time specified in Section 7.7.2 and Appendix G. If at Visit 1, Visit 2, if applicable, or Visit 6 the subject has not adhered to this restriction the reversibility assessment should be re-scheduled within the next 7 days; other assessments for the visit can be completed as planned.

Albuterol 90µg metered dose or Salbutamol 100µg metered dose will be used in the reversibility assessment. Up to 8 doses may be administered at Visit 1, Visit 2 and 6 for run-in reversibility, and up to 4 doses at the other visits (Visits 12, 26 and IPD). Up to 4 doses will be administered at Visit 1 for subjects with the historical reversibility and Visit 6 if the reversibility criterion has been met at Visit 1 or for subjects with the historical reversibility. If there is any concern about the effect on the subject's heart rate, tremor or any other safety parameter during the assessment fewer doses can be administered; the reason should be noted in the subject's medical records.

A spacer device should be used for administration of the SABA; nebulizers should not be used. The same bronchodilator and type of device should be used at each visit where reversibility is assessed.

Step 1: FEV1 measurement after 4 SABA inhalations

For administration of albuterol/salbutamol, the subject will:

i. Perform a gentle, complete expiration

ii. Inhale Dose 1 of the SABA to TLC and hold their breath for 5-10 seconds before the subject exhales.

iii. Rest for approximately 30 seconds before the next dose

iv. Repeat this for Dose 2, Dose 3 and Dose 4, resting for a further 15 – 20 minutes after Dose 4.

After resting for 15 – 20 minutes FEV1 is measured following the technique described in Section 5.1.4.

Visit 1, Visit 2 and Visit 6: if the inclusion criterion for reversibility is met (≥12% and ≥200 mL) or at Visit 1 for the subjects with the historical reversibility, this is the end of the reversibility assessment/post-BD FEV1 assessment. If it is not met the subject proceeds to Step 2.

Visit 12, Visit 26 and IPD Visit: this is the end of the post-BD FEV1 assessment.

Step 2: FEV1 measurement following a further 2 (total of 6) SABA inhalations (Only at Visit 1, Visit 2 and Visit 6, if assessed)

The subject will repeat the SABA inhalation procedures for Dose 5 and Dose 6. (See Step 1 above for instructions.)

After resting for the 15 – 20 minutes FEV1 will be measured following the technique described in Section 5.1.4

This is the end of the reversibility assessment if either of the following occurs:

- the inclusion criterion for reversibility is met (≥12% and ≥ 200 mL) or
- the incremental change in FEV1 between Step 1 and 2 is ≤ 5% and the inclusion criterion is not met

Subjects proceed to Step 3 if the incremental change in FEV1 between Step 1 and Step 2 is >5% and if the criterion for reversibility has not yet been met.

Step 3: FEV1 measurement following a further 2 (total of 8) SABA inhalations (Only at Visit 1, Visit 2, and Visit 6 if assessed)

The subject will repeat the inhalation procedures for Dose 7 and Dose 8, resting for 15 – 20 minutes after Dose 8. (See Step 1 above for instructions.)

After resting for the 15 – 20 minutes FEV1 will be measured following the technique described in Section 5.1.4. The reversibility assessment is now complete.

For subjects who need to perform step 2 and/or step 3 of the reversibility testing at Visit 6, the baseline value for the post-BD outcome variable in FEV1 will be derived from the value obtained after step 1.

5.1.5 Home PEF testing

An electronic, hand-held spirometer (peak flow meter) will be provided to the subject at Visit 1.

Home PEF testing will be performed by the subject in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Recording of home PEF should start from the evening of Visit 1 until the morning of Visit 26 (Week 40) using an ePEF meter device. When possible, ambulatory lung function measurements should be taken at least 6 hours after the last dose of SABA rescue medication.

Subjects should perform 3 successive peak flow manoeuvres while sitting or standing, but in the same position at every testing; the highest of the 3 values will be captured for the morning and for the evening manoeuvres.

The Investigator/authorized delegate will check subject's adherence to correct use of the peak flow meter at each visit as shown in Table 1 and Table 2 (or at the EOT visit if prematurely discontinued from the study).

5.1.6 Safety assessments

5.1.6.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at visits in accordance with the schedule outlined in Table 1 and Table 2. Haematology and clinical chemistry samples should be collected at unscheduled visits for assessing an asthma exacerbation, at a minimum. Other unscheduled visits may be initiated as needed, and assessments performed as per investigator's judgement. For dosing visits, all samples will be taken prior to the administration of IP.

Detailed schedules of the chemistry, haematology, and urinalysis tests are presented in Table 5, Table 6, Table 7, and Table 8, respectively.

Table 5 List of safety laboratory tests

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum)
B-Haemoglobin	S-Alkaline phosphatase (ALP)
B-Leukocyte count	S-Alanine transaminase (ALT)
B-Leukocyte differential count (absolute count)	S-Aspartate transaminase (AST)
B-Platelet count	S-Bilirubin, total
B-Hematocrit	S-Blood urea nitrogen
B-Mean corpuscular volume	S-Calcium, total
B-Red blood cell (RBC) count	S-Carbon dioxide (CO_2)
	S-Chloride
	S-Creatinine
	S-Creatinine kinase
Urinalysis	S-CRP
U-Nitrite,Bilirubin, Glucose, Blood, Protein, Ketones (dipstick)	
Urine microscopy and urine casts (as required)	
Urine culture (as required)	S-Gamma-glutamyl transpeptidase (GGT)
	S-Glucose
	S-Phosphorus
	S-Potassium
	S-Sodium
	S-Total cholesterol
	S-Uric acid

Table 6 Clinical chemistry tests schedule

Visit	V1	V6 (Rand)	V12	V22	V26	IPD
Week	**-10**	**0**	**12**	**32**	**40 (EOT)**	
ALP	X	X	X	X	X	X
ALT	X	X	X	X	X	X
AST	X	X	X	X	X	X
BUN	X	X	X	X	X	X
Calcium, total		X			X	X

Visit	**V1**	**V6 (Rand)**	**V12**	**V22**	**V26**	**IPD**
Week	**-10**	**0**	**12**	**32**	**40 (EOT)**	
Chloride		**X**			**X**	**X**
CO_2		**X**			**X**	**X**
Creatinine	**X**	**X**	**X**	**X**	**X**	**X**
Creatinine kinase		**X**				
CRP		**X**				
GGT	**X**	**X**	**X**	**X**	**X**	**X**
Glucose		**X**			**X**	**X**
Phosphorus		**X**			**X**	**X**
Potassium		**X**			**X**	**X**
Sodium		**X**			**X**	**X**
Total bilirubin	**X**	**X**	**X**	**X**	**X**	**X**
Total cholesterol		**X**			**X**	**X**
Uric acid		**X**			**X**	**X**

Table 7 Haematology/Haemostasis (whole blood) schedule

VISIT	V1	V6 (Rand)	V7	V8	V10	V12	V14	V16	V18	V20	V22	V24	V26	V27	V28	IPD
Week	**-10**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**54**	
B-Haemoglobin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-Leukocyte count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-Leukocyte differential count (absolute count)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-Platelet count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-Hematocrit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-Mean corpuscular volume	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-Red blood cell count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 8 Urinalysis schedule

VISIT	V1	V6 (Rand)	V12	V22	V26	IPD
Week	**-10**	**0**	**12**	**32**	**40 (EOT)**	
U-Nitrite,Bilirubin, Glucose, Blood, Protein, Ketones (dipstick)	X	X	X	X	X	X
Urine microscopy and urine casts (as required)*						
Urine culture (as required)*						

***** Urine samples will be collected and sent for analysis at the central lab only when a positive dipstick result for any parameter is observed.

The total volume of blood that will be collected from each subject during the study is presented in Table 9.

Table 9 Volume of blood to be drawn from each subject

Assessment[3]		Sample volume (mL)	No. of samples	Total volume[2] (mL)
Safety	Clinical chemistry	2.5	5	12.5
	Haematology	2	15	30
FSH, β-HCG[1]		1	1	1
Serology		7.5	1	7.5
IgE		2.5	2	5.0
Phadiatop		2.5	1	2.5
Serum Biomarkers		16	8	128
ADA/nAb		3.5	4	14
PK		3.5	6	21
Total				221.5

1 Female subjects only

2 The number of samples may be changed due to additional sampling at IPD, unscheduled visits, and the blood volume required may be altered to fit the assay requirements. The total volume of blood drawn from each subject over the course of the study will not exceed 450 ml.

3 Timing of Assessments as per Tables 1 and 2

Blood samples for determination of haematology/haemostasis and clinical chemistry will be performed at a central laboratory. For information on methods of collection, assessment, labeling, storage and shipment of samples please refer to the separate Laboratory Manual.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results report should be signed and dated, and retained at site as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix D, 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

5.1.6.2 Pregnancy Test

The following tests are applicable to female subjects only, and will be conducted in accordance with the schedule provided in Table 1 and Table 2.

- Serum β-human chorionic gonadotropin (ß-HCG) – the test done at enrolment (Visit 1) only, for WOCBP and adolescent females (analyzed at central laboratory)

- FSH – the test done at enrolment (Visit 1) only, for female subjects to confirm postmenopausal status in women <50 years who have been amenorrheic for 12 months or more

- Urine HCG – the test will be performed at the study site for WOCBP and adolescent females at each treatment visit before IP administration using a dipstick. Positive urine test result must be confirmed with serum β-HCG.

5.1.7 Physical examination

Physical examinations (complete and brief) will be performed in accordance with schedule provided in Table 1 and Table 2.

Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE as described in section 6.1.

5.1.7.1 Complete physical examination

The complete physical examination will include an assessment of the following: general appearance, skin, head and neck (including eyes, ears, nose, mouth, and throat), lymph nodes, abdomen, musculoskeletal (including spine and extremities), cardiovascular, respiratory, and neurological systems.

5.1.7.2 Brief physical examination

The brief physical examination will include an assessment of the general appearance, abdomen, cardiovascular and respiratory system. For the brief physical examination only, information on whether the assessment was performed or not will be recorded.

5.1.8 dECG

All ECG assessments must be performed using a digital electrocardiogram (dECG) device.

Digital ECGs will be performed in accordance with schedule provided in Table 1 and Table 2.

Digital ECG assessments will be performed prior to blood drawing, spirometry, IP administration and BD administration.

For all subjects, the printouts of the dECG will be collected and signed, dated and stored at the study site along with a signed and dated photocopy of each printout (ie, if the printout is not on archive-quality paper).

5.1.8.1 Resting 12-lead dECG

A 12-lead dECG will be taken in supine position, after the subject has been resting for at least 5 minutes. The assessment should be performed before interventions with the subject (eg, spirometry and administration of asthma-related medications and IP).

A standard dECG with a recommended paper speed of 50 mm/second covering at least 6 sequential beats will be used. The Investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential dECG findings. In case of discrepancy between the Investigator's interpretation and that provided by the dECG machine (if applicable), the Investigator's interpretation takes precedence and should be noted on the printout and recorded in the eCRF. Two identical copies of the dECG will be produced and quality checked and kept in case of further need for re-evaluation.

It is highly recommended that the same machine be used for all dECG assessments throughout the subject's participation in the study.

dECG data and evaluation will be performed by the site Investigator and recorded in the eCRF.

5.1.9 Vital signs

Vital signs (i.e., pulse, blood pressure, respiration rate and body temperature) will be obtained in accordance with the schedule provided in Table 1 and Table 2. Vital signs will be taken prior to blood drawing, IP administration, and, if possible, usual asthma controller medication. At Visits 6 through 9, subjects should be observed for a minimum of 2 hours after IP administration for the appearance of any acute drug reactions. For the remaining visits involving IP administration, subjects will be observed for a minimum of 1 hour after IP administration for any such reaction.

Vital signs should also be taken prior to BD administration, if applicable for that visit.

Pulse, blood pressure and respiration rate

Pulse rate and blood pressure should be measured after the subject has been resting for at least 5 minutes. The measurement will be taken in sitting position. Pulse rate will be obtained before blood pressure.

Respiration rate will be obtained after subject has been resting for at least 5 minutes, by counting number of breaths (ie, how many times the chest rises) for one minute.

Body temperature

Body temperature will be measured in degrees Celsius prior to IP administration, in accordance with local standards.

5.1.10 Other safety assessments

5.1.10.1 Serology

Hepatitis B surface antigen, hepatitis C antibody, HIV-1 and HIV-2 antibodies will be assessed at enrolment (Visit 1) only. All testing for these will be performed at a central laboratory.

Instructions for sample collection, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

5.1.10.2 Infections

Subjects experiencing serious infections, defined as life-threatening infections, infections requiring hospitalization, or infections requiring treatment with antiviral medications, intravenous antibiotics or medications for helminth parasitic infections or that lead to a permanent discontinuation of study drug should be noted in the infection module in the eCRF.

5.2 Other assessments

5.2.1 Weight and height

Weight and height will be measured in accordance with the schedule provided in Table 1 and Table 2.

Height will be measured at enrolment (Visit 1) for all subjects and at Visit 26 (EOT) and IPD visit for adolescents only.

The subject's weight will be recorded in kilograms, and height will be recorded in centimetres. Weight and height measurements will be performed in light clothing and with shoes off.

5.2.2 Patient reported outcomes

Patient reported outcomes data will be captured using an ePRO. The device will be paired with a handheld spirometer (peak flow meter) for measuring at-home PEF testing (as outlined in section 5.1.5). Subjects will be trained on at-home use of the ePRO and handheld spirometer at Visit 1. Training will include explanation of device functionality and proper use of the spirometer. The subject will be asked to use both devices as part of the training and will be asked to verify completion of training on the ePRO device. Subjects will be provided with information on device use and issue resolution (eg, helpdesk numbers) to conclude the training. The site staff will set assessment reminder alarms on the device and the subject will complete the ACQ-6 at Visit 1. At-home PRO assessment will start the evening of Visit 1. Subjects will be asked to bring the device back at each study visit. At Visit 6 subjects will complete non-daily PROs on the device to start the visit for the baseline assessments at the site. Following Visit 6, all PRO data will be collected at home until Visit 26. Additional details concerning the assessments can be found in the subsequent sections (see sections 5.2.2.1 to 5.2.2.5).

5.2.2.1 Asthma Daily Diary

The Asthma Daily Diary will be completed each day from the evening of Visit 1 to the morning of Visit 26. The Asthma Daily Diary will include the following daily recordings: morning and evening home PEF data (obtained from the home peak flow meter), asthma symptoms, inhalations of rescue medication, nights with awakenings due to asthma symptoms, maintenance medication compliance. There will be triggers in the ePRO device to alert the subjects to signs of worsening of asthma and to contact their physician, please refer to section 5.1.1.

The subject should contact the investigator for evaluation after receiving a diary alert. The Investigator/authorized delegate will check subject's adherence to the Asthma Daily Diary at each visit as shown in Table 1 and Table 2.

Home PEF measurement

Details regarding home PEF measurement please refer to section 5.1.5.

Asthma symptoms

Asthma symptoms during night-time and daytime will be recorded by the subject each morning and evening in the Asthma Daily Diary, beginning the evening of Visit 1 until the morning of Visit 26.

Daytime is defined as the time period between the morning lung function assessment (upon rising in the morning) and the evening lung function assessment. Night-time is defined as the time period between the evening lung function assessment (at bedtime) and the morning lung function assessment.

Rescue medication

The number of rescue medication inhalations (puffs) and nebulizer treatments taken will be recorded by the subject in the Asthma Daily Diary twice daily (ie, in the morning and evening) beginning the evening of Visit 1 until the morning of Visit 26. The number of inhalations taken between the morning and evening lung function assessments will be recorded in the evening. The number of inhalations taken between the evening and the morning will be recorded in the morning.

Nocturnal awakenings

Nocturnal awakenings due to asthma symptoms will be recorded by the subject in the Asthma Daily Diary each morning, beginning in the morning after Visit 1 until the morning of Visit 26, by answering question whether he/she woke up during the night due to asthma symptoms by a "yes" or "no" response.

Maintenance medication

Maintenance medication and OCS compliance will be captured daily from the evening of Visit 1 until the morning of Visit 26. Maintenance medication (non-OCS) will be recorded in the Asthma Daily Diary once daily in the morning. The maintenance medication question will ask about compliance with regularly scheduled asthma medications taken "yesterday". The response options will be: "Yes, I took all doses as scheduled"; "No, I did not take any of the doses scheduled"; and "I took some but not all scheduled doses". The question will instruct respondents to not consider their rescue medication or OCS when answering. During device training, sites will instruct subjects that they should only consider their non-OCS controller medication when answering this question. Compliance with OCS will be captured via a separate question in the evening diary. The OCS compliance question will have the following response options: "yes", "no, dose was missed", not scheduled today" or "not applicable, dose reduced to 0".

5.2.2.2 Asthma Control Questionnaire (ACQ-6)

The ACQ-6 is a shortened version of the ACQ that assesses asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and short-acting β_2-agonist use) omitting the FEV_1 measurement from the original ACQ score.

Subjects will be asked to recall how their asthma has been during the previous week by responding to 1 question regarding their BD use, and 5 questions pertaining to their asthma symptoms.

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and ≤ 1.5 indicate partly controlled asthma, and a score >1.5 indicates uncontrolled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered to be clinically meaningful.

The questionnaire will be completed using the ePRO device.

An initial screening ACQ-6 will be taken at Visit 1 at the study site, then every 14 days (± 1 day) throughout the enrolment (Visit 1), run-in/optimization period. Subjects will then complete the ACQ-6 at Visit 6, and once randomized, subjects will be asked to complete ACQ-6 once every 14 days (± 1 day) throughout the treatment period, until the EOT visit where the ACQ-6 will be completed at the site.

The Investigator/authorized delegate will check the subject's adherence to the ACQ-6 at each visit as shown in Table 1 and Table 2.

5.2.2.3 Standardised Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(S)+12)

The AQLQ(S)+12 is a questionnaire that measures health related quality of life , developed for asthma subjects ages 12 and above.

The questionnaire comprises 4 separate domains (ie, asthma symptoms, activity limitations, emotional function, and environmental stimuli).

Subjects will be asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score will be calculated as the mean response to all questions. The 4 individual domain scores (symptoms, activity limitations, emotional function, and environmental stimuli) are the means of the responses to the questions in each of the domains. Individual improvement in both the overall score and individual domain scores of 0.5 has been identified as a minimally important change. The questionnaire will be completed using the subject's ePRO device.

The AQLQ(S)+12 will be first completed by the subject at the site at Visit 1, then every 14 days (± 1 day) throughout the enrolment (Visit 1), run-in/optimization period. Subjects will then complete the AQLQ(S)+12 at Visit 6, and once randomized, subjects will be asked to complete AQLQ(S)+12 once every 28 days (± 1 day) throughout the treatment period, until the EOT visit where this will be completed at the site.

The Investigator/authorized delegate will check the subject's adherence to AQLQ(S)+12 at each visit as shown in Table 1 and Table 2.

5.2.2.4 Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ)

The WPAI+CIQ consists of questions about how asthma and asthma related issues impact a subject's ability to work, attend classes, and perform regular daily activities. The questionnaire relates to the subject's experience over the previous 7 days. The WPAI+CIQ will be used to measure self-reported productivity loss. The questionnaire will be completed using the subject's ePRO device.

The WPAI+CIQ will be first completed at Visit 6 (Week 0), then every 2 weeks (±1 day) at home throughout the 40 week treatment period.

The Investigator/authorized delegate will check subject's adherence to WPAI+CIQ at each visit as shown in Table 2.

5.2.2.5 European quality of life-5 dimensions-5 levels (EQ-5D-5L)

The EQ-5D-5L 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 by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, 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 EQ-5D-5L will be completed weekly (+1 day) starting from Visit 6 (Week 0) throughout Week 40 (Visit 26) using the ePRO device.

The Investigator/authorized delegate will check subject's adherence to EQ-5D-5L at each visit as shown in Table 2.

5.2.2.6 Health care resource utilization

Broad-based health care utilization due to asthma-related event information will be collected by the Investigator/authorized delegate (as shown in Table 1 and Table 2) and recorded in the appropriate eCRF module.

At Visit 1, Healthcare Resource Utilization (HRU) information will be collected with a 'one year' recall period. All the subsequent visits will collect HRU information with a recall period of 'since the last scheduled visit'.

Note: cases of hospitalization must also be reported as an SAE (as described in sections 6.2 and 6.4).

5.3 Pharmacokinetics and Immunogenicity

5.3.1 Collection of samples

Blood samples for determination of tralokinumab in serum will be collected pre-dose at the times presented in Table 1 and Table 2. It is important that date and time of each SC injection and sample collection be recorded for each subject.

Instructions for sample collection, labeling, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

The volume of blood that will be collected from each subject for these assessments is presented in Table 9.

5.3.2 Determination of drug concentration

Samples for determination of tralokinumab concentration in serum will be analyzed by a laboratory on behalf of AstraZeneca, using a validated bioanalytical method. Details of the analytical method used will be described in a bioanalytical report. The PK samples will be retained for future use at AstraZeneca, or designee, for a maximum of 15 years following the date of Last Subject Last Visit.

A summary of PK analysis results will be reported in the CSR; details of the PK analysis will be reported separately in a bioanalytical report.

5.3.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical Report.

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to the AstraZeneca Biobank; see details in the Laboratory Manual).

5.3.4 Immunogenicity

Instructions for immunogenicity (ADA and nAb) sample collection, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

Samples used for immunogenicity analyses will be retained at AstraZeneca or designee for a maximum of 15 years following the Last Subject's Last Visit. A summary of the analysis will be presented in the CSR. Details of the analytical method used will be described in a bioanalytical report.

Anti-tralokinumab antibodies

The pre-dose serum samples to measure presence of ADA will be collected according to the schedule of study procedures (see Table 2).

The presence or absence of ADA will be determined in the serum samples using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step.

Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination and will be analyzed for the presence of nAb.

Neutralizing antibodies

Neutralizing antibodies will be assessed as per Table 2 according to the tiered testing scheme outlined above, as well as at any discontinuation, as indicated.

The presence or absence of nAb will be determined using a validated bioanalytical method. A summary of nAb incidence rate will be reported in the CSR and details of the nAb assessment will be reported separately in a bioanalytical report.

5.3.5 Total IgE

Testing for total IgE will be performed at Visits 6 and 26 (Weeks 0 and 40, respectively).

Instructions for sample collection, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

5.3.6 Phadiatop (Allergy Screen)

Testing for phadiatop (allergy screening test) will be performed at Visit 6 (Week 0). The analysis for this test will be managed by the central laboratory.

Instructions for sample collection, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

5.4 Pharmacodynamics

5.4.1 Serum biomarkers

Blood (serum) samples will be collected pre-dose according to the schedule in Table 1 and Table 2 to evaluate the pharmacology of tralokinumab, including but not limited to, periostin and DPP4. Instructions for sample collection, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites. AstraZeneca or a designee will retain serum biomarker samples for investigation of the pharmacology of tralokinumab for a maximum of 15 years following the last subject's last visit.

The results from the investigation of such samples may not be reported in the CSR but in separate reports and in scientific publications as appropriate.

5.4.2 Level of fractional exhaled nitric oxide

Method of assessment

Fractional exhaled nitric oxide (FE_{NO}) measurements will be performed at Visits 1, 6, 8, 10, 12, 18, 22, 26 (see Table 1 and Table 2). Subjects should not use their rescue SABA medication (eg, albuterol/salbutamol) within 6 hours of the measurement. Inhaled BDs,

including ICS/LABA combinations should be withheld for the effect duration specific to the BD (see Appendix G) prior to all visits. If not, the visit must be rescheduled.

Measurements will not be performed until 2 weeks after a respiratory infection. Subjects will be asked whether they have had a respiratory infection in the 2 weeks prior to measurement, which will be recorded as "Yes or No" in the eCRF. Measurement of (FE_{NO}) will be performed prior to the spirometry measurements.

FE_{NO} will be measured using an electrochemical sensor. Information concerning the specifications and use of the analyzer will be provided in a separate instruction manual.

The standard single exhalation technique recommended by the ATS will be followed (Dweik et al 2011).

Signed and dated printouts from the measurements will be kept in the ISF for Source Data Verification (SDV). Printouts will be marked with the study code, subject enrolment/ randomization code, date, time of measurement, visit number and subject initials. If a printout cannot be printed, the mean value of the measurements will be recorded in the subject's medical records for SDV.

The vendor supplying the chemiluminescence analyzer to participating sites will be responsible for ensuring that the equipment and procedures for the measurement of FE_{NO} are validated prior to the start of the study.

5.5 Pharmacogenetics (Not Applicable)

5.6 Biomarker analysis

The subject's consent or assent to the use of donated biological samples for non-exploratory analysis purposes is mandatory.

Biological samples (ie, blood, plasma, serum) will be collected and may be analyzed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

5.6.1 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

5.6.2 Labelling and shipment of biological samples

The Principal Investigator will ensure that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials will not be shipped and no further samples will be taken from the subject unless agreed with AstraZeneca, and appropriate labelling, shipment and containment provisions are approved.

5.6.3 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their lifecycle.

The Principal Investigator, or delegate, at each site will keep full traceability of collected biological samples from the subjects while in storage at the site until shipment or disposal (where appropriate), along with documentation of receipt of arrival.

The sample receiver will keep full traceability of the samples while in storage and during use until used, or disposed of, or until further shipment along with documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

Samples retained for further use will be registered in the AstraZeneca Biobank during their entire life cycle.

5.6.4 Withdrawal of Informed Consent or Assent for donated biological samples

If a subject withdraws consent or assent to the use of their donated biological samples that will be used for non-exploratory purposes, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research. As collection of the biological samples that will be used for non-exploratory purposes, is an integral part of the study, the subject will be withdrawn from further study participation. Subjects who withdraw their consent/assent for the use of their samples to be used for exploratory/future use purposes, will be allowed to continue in the study.

The Principal Investigator will be responsible for ensuring that:

The subject's withdrawal of informed consent or assent to the use of donated samples is notified immediately to AstraZeneca

The biological samples from any subject who withdraws consent or assent to the use of these samples, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented

The laboratory(ies) holding the samples is/are informed about the withdrawn consent or assent immediately, and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site

The subject and AstraZeneca are informed about the sample disposal.

AstraZeneca will ensure that the central laboratory(ies) holding the samples is/are informed about the withdrawn consent or assent immediately, the samples are disposed of/destroyed, and that the action is documented and provided to the study site.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study period (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events, including SAEs will be collected from the time the subject signs the informed consent or assent form, throughout the treatment period and the follow-up periods (ie, Visit 28, Week 54).

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at any follow up visit in the study will be followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Adverse event variables

The following variables will be collected in the eCRF for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity* of the AE
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to IP
- AE caused subject's withdrawal from study *(*yes or no*)*
- Outcome

*Intensity rating scale:

1 mild (awareness of sign or symptom, but easily tolerated)
2 moderate (discomfort sufficient to cause interference with normal activities)
3 severe (incapacitating, with inability to perform normal activities)

In addition, the following variables (if applicable) will be collected in the eCRF for SAEs:

- Date AE met criteria of serious

- Date Investigator became aware of the SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Description of the AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Assessment of causality

The Investigator will assess causal relationship between the IP and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is provided in Appendix B to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *'Have you/your child had any health problems since the previous visit/you were last asked'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other

signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator will use the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.7 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Disease progression

Symptoms of the disease under study

Asthma symptoms or signs, such as, wheeze, cough, chest tightness, dyspnoea, breathlessness and phlegm, will be recorded as AEs when:

- the sign or symptom is serious according to definitions, see Section 6.2,
- the subject discontinues the study due to the sign or symptom, and/or
- the sign or symptom is new to the subject or not consistent with the subject's pre-existing asthma history (defined as within 1 year of Visit 1) as judged by the Investigator.

Asthma exacerbations should not be recorded as AEs, unless it fulfils any of the above criteria. All asthma exacerbations should be recorded in the exacerbation eCRF as per Section 5.1.3.

If a subject discontinues IP due to a study specific discontinuation criterion, this should always be recorded as 'Development of study specific withdrawal' on the termination form in the eCRF. In addition, the Investigator must assess whether the asthma deterioration should also be reported as an AE leading to discontinuation of IP (DAE)/AE leading to withdrawal from study on the AE form.

6.4 Reporting of serious adverse events

All SAEs must be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs during the course of the study, Investigators or other site personnel must inform the appropriate AstraZeneca representatives within one day (ie, immediately) but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Subject Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs, where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel must inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day (ie, immediately) but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert will be sent to the designated AstraZeneca representative(s).

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative(s) by telephone.

The AstraZeneca representative(s) will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca IP.

6.5 Overdose

An overdose with associated AEs is to be recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF, as well as in the Overdose eCRF module.

An overdose without associated symptoms is only to be reported on the Overdose eCRF module.

If an overdose with the AstraZeneca study drug occurs during the course of the study, the Investigator, or other site personnel, must inform appropriate AstraZeneca representative(s) immediately, and **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Subject Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel will inform the appropriate AstraZeneca representatives within 1 day (ie, immediately) but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Subject Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy module in the eCRF will be used to report the pregnancy and the pregnancy outcome module will be used to report the outcome of the pregnancy.

6.6.2 Paternal Exposure

There is no restriction on fathering children or donating sperm during the study.

6.7 Management of IP related toxicities

Appropriate drugs, such as epinephrine, H1 and H2 antihistamines, and corticosteroids, as well as medical equipment to treat acute anaphylactic reactions must be immediately available

when IP is being administered. Study site personnel must be trained to recognize and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix F.

Anaphylaxis will be defined as serious reaction that is rapid in onset and may cause death (Sampson et al 2006). Anaphylaxis typically manifest as 1 of 3 clinical scenarios:

1. The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and at least one of the following: a) respiratory compromise; or b) reduced blood pressure or symptoms of end-organ dysfunction

2. Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms and/or persistent gastrointestinal symptoms

3. Reduced blood pressure after exposure.

Subjects will have had a pre-assessment (ie, vital signs and lung function) prior to IP administration. At Visits 6 through 9, subjects should be observed for a minimum of 2 hours after IP administration for the appearance of any acute drug reactions. For the remaining visits involving IP administration, subjects will be observed for a minimum of 1 hour after IP administration for any such reaction.

In order to help understand the potential drug-relatedness of any acute reaction, a blood sample should be drawn during the event for additional ADA testing (if not already scheduled for this visit). If an anaphylactic reaction occurs, a blood sample will be drawn from the subject as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge for analysis of serum tryptase. The sample will be tested at the local lab or central laboratory where applicable.

6.8 Study governance and oversight

6.8.1 Independent Adjudication Committee

Tralokinumab is being developed for the treatment of severe asthma. There is considerable variation in the severity of subjects who seek ER or urgent care, and in the clinical thresholds used to determine the need for hospitalization.

An independent adjudication committee, blinded to the treatment of the subjects, will evaluate cases of ER or urgent care visits and hospitalizations, as well as all deaths, that occur during the course of the study to confirm that any such event is due to a worsening of asthma. For completeness, the adjudication committee will also be tasked with reviewing cardiovascular, cerebrovascular and malignant adverse events occurring after randomization. The committee will include specialists in pulmonology, cardiology, neurology and oncology and will operate in accordance with dedicated Adjudication Committee Charter/Manual of Operations.

6.8.2 Data and safety monitoring board

An external DSMB will monitor and protect the safety of adolescent subjects throughout the double blind treatment period of the study. The DSMB members will be selected for their expertise. The voting members of the DSMB will be comprised of external individuals including the DSMB chair. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or subjects.

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. Subject enrollment will continue during DSMB review of safety data.

The DSMB will operate in accordance with the dedicated DSMB Charter/Manual of Operations and will be agreed to in advance by the DSMB members.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

The IP will be manufactured in accordance with Good Manufacturing Practice (GMP).

Tralokinumab and placebo administered in the study will be a clear to opalescent, colourless to yellow solution free from, or practically free, from visible particles.

Subjects will be randomized in a 1:1 ratio to receive 300 mg tralokinumab or placebo every 2 weeks.

Each subject will receive two SC injections of 150 mg tralokinumab at each dosing interval to receive a total dose of 300 mg, or placebo. The identity details for the IP are found in Table 10.

Table 10 Identity of investigational product

Investigational product	Concentration and Formulation	Dosage form and strength	Manufacturer
Tralokinumab	Formulated at a nominal concentration of 150 mg/mL in 50mM sodium acetate/acetic acid buffer, 85mM sodium chloride, 0.01% (w/v) PS-80 pH 5.5 solution.	150 mg/mL solution for injection in an accessorized pre-filled syringe, 1.0 mL fill volume.	MedImmune
Placebo	Placebo contains the same excipients, in the same concentration only lacking tralokinumab	Placebo solution for injection in an accessorized pre-filled syringe, 1.0 mL fill volume.	MedImmune

The accessorized pre-filled syringe (APFS) is a single use, disposable system that is designed to administer the labelled dose of the system to the subcutaneous space during one injection and automatically provide a safety mechanism to reduce the occurrence of accidental needle sticks during disposal of the system.

The APFS consists of a pre-filled syringe sub-assembly (PFS-SA; 1 mL fill volume, pre-filled syringe barrel with a 27 gauge thin wall, 1/2 inch long staked in needle, rigid needle shield, plunger stopper) and a safety device.

7.2 Dose and treatment regimens

The IP will be administered at the study site on treatment visits and within visit windows as specified in Table 2.

IP administration

IP will be administered by a qualified, unblinded healthcare professional. The two injections should be administered within the same body location, separated by at least 3 cm. The injection site must be recorded in the source documents at each treatment visit and recorded in the eCRF.

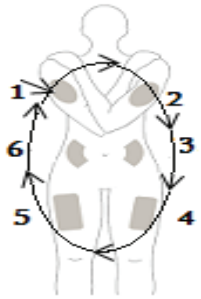
IP **must** be equilibrated to room temperature for a minimum of 30 minutes prior to dose administration.

The person administering the dose will wipe the skin surface of the upper arm, anterior thigh or abdomen with alcohol, and allow to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be inserted at a 90-degree angle approximately

halfway into the SC tissue. The IP will be slowly injected (at least 5-second duration is recommended) into the SC tissue using gentle pressure. The area should not be massaged after injection.

It is advised that the site of injection of IP be rotated such that the subject receives IP at a different anatomical site at each treatment visit. The suggested injection site rotation sequence is presented below in Figure 3.

Figure 3 Injection sites and rotation scheme



In cases when rotation of the injection site is not favorable for the subject and/or Investigator, the injection site, along with the reason why the site was changed, should be recorded in the source documents and eCRF for each such occurrence.

Further details on IP administration are provided in the IP Handling Instructions. IP administration must be carried out according to these instructions.

After IP administration

Subjects will have had a pre-assessment (i.e., vital signs and lung function) prior to IP administration. At Visits 6 through 9, subjects should be observed for a minimum of 2 hours after IP administration for the appearance of any acute drug reactions with vital signs taken every 30 minutes or until stable, whichever is later. For the remaining visits involving IP administration, subjects will be observed for a minimum of 1 hour after IP administration for any such reaction with vital signs taken every 30 minutes or until stable, whichever is later.

Conditions requiring IP administration rescheduling

If any of the following should occur, the Investigator should reschedule the visit and IP should not be administered until the rescheduled visit:

- The subject has an intercurrent illness, that in the opinion of the Investigator may compromise the safety of the subject in the study (eg, viral illnesses)

- The subject, in the opinion of the Investigator, is experiencing an acute or emerging asthma exacerbation

- The subject is febrile (defined as ≥38°C; ≥100.4°F) within 72 hours prior to IP administration

7.3 Labelling

Labelling of the IP will be carried out by AstraZeneca or designee in accordance with Annex 13 and current GMP and regulatory requirements of each country participating in the study. The labels will be translated into local languages where applicable and required by local regulations.

7.4 Storage

Tralokinumab/placebo is to be stored at the study site in a secured facility with limited access and controlled temperature. The temperature should be monitored on daily basis and documented in the temperature monitoring log.

The IP must be kept in the original outer container and under conditions specified on the label.

In the following cases:

- Temperature excursion upon receipt or during storage at the study site
- Damaged kit upon receipt, or
- Damaged syringe/cartridge,

site staff should not use the affected IP, and should immediately contact their AstraZeneca representative for further guidance. Damaged IP should be documented via IWRS/IVRS (please refer to the IWRS/IVRS manual for further details).

7.5 Compliance

The date and time of all IP administrations, as well as any missed doses, should be recorded in the appropriate section of the eCRF.

7.6 Accountability

The study drugs provided for this study will be used only as directed in the protocol.

It is the Investigator's responsibility to ensure that a procedure is established and maintained for the operation of the unblinded study drugs, this includes but is not limited to:

- The study drugs are administrated only by a qualified, unblinded health professional named in the delegation of responsibility log.
- An unblinded health professional will account for all study drugs dispensed to the subjects.

An unblinded health professional, if applicable, or the blinded AstraZeneca monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery and destruction should be signed.

In case of malfunctioning APFS, the centre should contact the unblinded AstraZeneca monitor to initiate a product complaint process according to applicable guidelines.

7.7 Concomitant and other treatments

7.7.1 Concomitant medications

Information about any treatment in the 3 months prior to the date of the informed consent and all the concomitant treatments given during the study, with reason for the treatment, will be collected by the Investigator/authorized delegate at each visit and recorded in the Electronic Case Report Form (eCRF).

Note: to satisfy inclusion criteria 6 and 7, the history of continuous treatment with high-dose ICS/LABA for at least 3 months prior to Visit 1 and use of OCS for at least 6 months prior to Visit 1 should be documented in source and recorded in the eCRF.

Oral corticosteroids

For eligibility purposes all subjects are required to be treated with OCS for at least 6 months prior to Visit 1 and be on the stable maintenance dose for at least 1 month prior to Visit 1.

The dose of OCS will be titrated down during optimization and reduction periods of the study (OCS optimization and Reduction periods, for details see Section 5.1.2).

Subjects who have one or more documented OCS reduction failures as outlined in section 3.1 which define the optimized dose prior to Visit 1 are not required to proceed through the pre-randomization optimization period.

OCS medication is not regarded as an IP, but will be provided/reimbursed by AstraZeneca according to local regulations, in order to maintain appropriate oversight and access to this concomitant therapy.

Maintenance of asthma controller medication

All subjects are required to be treated with a stable dose of ICS corresponding to ≥500 µg fluticasone propionate dry powder formulation equivalents (as outlined in Appendix E) and LABA for at least 3 months prior to Visit 1 and during the treatment period. Subjects may also receive other physician prescribed asthma controller medications.

The aim of this study is to establish the treatment effect of tralokinumab as an add-on treatment and therefore the maintenance asthma controller therapy should be maintained at a stable dose from Visit 1 until the end of the treatment period, in order to prevent any independent confounding of the anticipated treatment effect of tralokinumab.

Changes to the subject's maintenance asthma controller medication regimen are discouraged during the treatment period, unless judged medically necessary by the Investigator. Ideally, such changes should be discussed with the AstraZeneca Study Team Physician, prior to any change being made.

All changes in the subject's maintenance medication should be documented in source along with rational for change and recorded in eCRF.

Maintenance medication is not regarded as an IP, but will be provided/reimbursed by AstraZeneca according to local regulations, in order to maintain appropriate oversight and access to this concomitant therapy.

Please note that subjects on maintenance treatment with theophylline should have documented blood concentration levels within therapeutic range. If this is not documented before signing the informed consent, it can be obtained after informed consent has been given or as part of the Visit 1 procedures. The sample can be analysed at the central or local lab as applicable.

Rescue medication

Salbutamol, albuterol, or levalbuterol will be used as rescue medication during the study in the event of a worsening of asthma symptoms. As with the maintenance ICS/LABA, rescue medication is not regarded as an IP, but will be provided/reimbursed by AstraZeneca according to local regulations, in order to ensure access to essential rescue therapy.

7.7.2 Restrictions during and after the study

7.7.2.1 Asthma medication restrictions

Use of short-acting β_2-agonists (SABA)

Regularly scheduled SABA use in the absence of any asthma symptoms is discouraged from enrolment (Visit 1) and throughout the study duration.

Prophylactic use of SABA (eg, prior to planned exercise) if deemed necessary by the subject and the Investigator, may be used, but should **not** be recorded in the Asthma Daily Diary. Any such use should be documented in medical notes and recorded in the eCRF.

SABA via a metered dose device is permitted as needed for worsening asthma symptoms (ie, rescue use) and will be recorded in the Asthma Daily Diary as number of inhalations.

Rescue use of SABA administered via jet or ultrasonic nebulization is allowed. Occasions where SABA was administered via nebulization will be recorded separately from metered dose inhaler inhalations in the Asthma Daily Diary.

Use of short acting anticholinergics

The use of short acting anticholinergics (eg, ipratropium) as a rescue treatment for worsening asthma symptoms outside of managing an asthma exacerbation event is not allowed from enrollment and throughout the study duration.

Use of long-acting β_2-agonists (LABA) as a reliever

The use of LABA as a reliever (eg, Symbicort maintenance and reliever treatment) is not allowed from enrollment and throughout the study duration.

Use of once daily bronchodilators and theophylline

Use of theophylline and once daily BDs is allowed at the discretion of the Investigator. These drugs should have been used at a stable dose for at least 3 months before Visit 1. A 48 hour minimum washout period for theophylline or once daily BDs is required before spirometry. Should the subject be taking theophylline or once daily BD in the evening, it is advised that the Investigator ask the subject to reschedule their theophylline or BD regimen to morning use, if there are no medical reasons to prevent this change.

It is important that a true pre-BD (ie, trough) FEV_1 reading obtained in order to maintain the integrity of planned efficacy analyses around lung function improvement. **Therefore, subjects will be asked to withhold from taking their usual regular BD medications and reliever SABA.** The subject's usual asthma controller medications may be administered, following completion of the pre-BD spirometry. The suggested order of administration of the subject's usual asthma controller, per protocol SABA (on visits where post-BD spirometry is assessed), and IP administration relative to scheduled pre and post-BD spirometry is given in section 5.1.4., for eligibility assessment (see Section 3.1, inclusion criteria 9 and 10). In case the subject does not meet the reversibility eligibility criteria, and a second re-test is done (not earlier than next calendar day and not later than 7 calendar days after the failed attempt), ICS/LABA medications can be withheld for 24 hours. In addition, SABA should not be used within 6 hours of these spirometry assessments. The subject's usual asthma medications may be administered following completion of the screening lung function procedures.

If the subject has taken their usual ICS/LABA and/or any other BD without the appropriate washout period before a site visit, the Investigator/authorized delegate should remind the subject of the importance of withholding their BD for an appropriate time and reschedule the visit for another day, within the allowed window.

If the subject has taken rescue SABA within 6 hours of the planned site visit spirometry they should ideally 1) remain at the site until such time that the 6 hour window has been reached or 2) return on another day, within the visit window.

Asthma medication restrictions prior to home PEF testing

Subjects should avoid taking their morning asthma controller medication prior to the morning home PEF testing, and should conduct the evening home lung function testing before taking evening asthma controller medication. When possible, home PEF testing, should be taken at least 6 hours after the last dose of SABA reliever medication

Asthma medication restrictions on unscheduled visits

Asthma medication restrictions on unscheduled visits may not be feasible, and may be applied at the discretion of the Investigator. Timing of recent controller and reliever SABA use relative to the unscheduled spirometry should be noted in the record.

Asthma medication restrictions at site visits with scheduled dECG assessment

Subjects should be instructed not to take their usual asthma controller medication prior to scheduled dECG assessment. Use of SABA should be avoided within 6 hours prior to the dECG assessment, use of twice daily LABA for 12-24 hours and theophylline or once daily BD for 48 hours.

The medication restriction is waived for the enrolment dECG at Visit 1.

7.7.2.2 Other medication restrictions

- Use of any off-label medications, for example medications locally approved for Chronic Obstructive Pulmonary Disease but not for asthma, are also not allowed from 30 days prior to Visit 1 and throughout the study.

- Use of immunosuppressive medication is not allowed (other than prior, stable OCS for the maintenance treatment of asthma).

- Receipt of live attenuated vaccines within 30 days prior to randomization and during the study, including the follow up period, is not allowed. Inactive/killed vaccines (eg, inactive influenza vaccine) are allowed provided they are not administered within 5 days before/after any dosing visit.

- Subject should not receive allergen immunotherapy injection on the same day as the IP administration

- Subjects should not take any other excluded medications:

  – Oral or ophthalmic non-selective β-adrenergic antagonist (eg, propranolol)

A table with medication-related restrictions is presented in Appendix G.

7.7.2.3 Bronchial Thermoplasty

Subjects should not undergo bronchial thermoplasty during the entire study.

7.7.3 Other treatments

Other treatments which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator. If any such treatment includes medications other than those described above, these medications are to be recorded in the appropriate section of the eCRF.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

The primary objective of this study is to show efficacy of tralokinumab vs. placebo with regards to reduction in the prescribed, daily, average, OCS maintenance dose. The primary

outcome variable is percent change from baseline in the daily OCS dose (primary) after 8 weeks of maintenance treatment following OCS dose reduction. Other outcome variables related to the reduction of the OCS maintenance dose are considered supportive to the primary variable.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first subject randomized and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data. Analyses will be performed by AstraZeneca or its representatives.

All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.

8.2 Sample size estimate

For sample size estimation purposes, the targeted difference in the percentage reduction of the OCS dose between the active and placebo is 50% (for example if the final OCS reduction from baseline in tralokinumab group is 75% and the final OCS reduction from baseline in the placebo group is 25%). Based on previous studies of OCS reduction an estimate of 80% was used for the standard deviation. Assuming a Type I error rate of 5% and at least 90% power, the sample size required is at least 55 subjects per treatment group.

8.3 Definitions of analysis sets

All efficacy analyses will be performed using an ITT approach based on the full analysis set. For consistency, demographic and baseline characteristics will be presented using the full analysis set. Safety objectives will be analyzed based on the Safety population.

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

8.3.1 Efficacy analysis set

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

8.3.2 Safety analysis set

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

8.3.3 PK analysis set

Pharmacokinetic analysis set (PK): All subjects in the full analysis set who received Tralokinumab. PK blood samples are assumed not to be affected by factors such as protocol deviations (eg, disallowed medication, or incorrect study medication received). All PK summaries will be based on this analysis set.

8.3.4 PRO analysis set

PRO outcome variables will be evaluated based on the full analysis set.

8.4 Outcome measures for analyses

8.4.1 General Definitions

8.4.1.1 Definition of baseline and subject baseline variables

The baseline OCS dose for the primary and secondary variables related to OCS reduction during the reduction and maintenance periods (Week 12 and onwards) is defined as the prescribed, daily, average dose prior to randomization (Visit 6)

For FEV_1 variables the measurement recorded at the randomization 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 FEV1, the measurement after the first BD administration will be used as baseline.

The baseline for ACQ-6, AQLQ(s)+12, WPAI-CIQ, and EQ-5D-5L will be captured on the ePRO device at Visit 6. Baseline for Asthma Daily Diary variables will be the bi-weekly mean for data collected between study day -14 and -1 (ie 14 to 1 day before Visit 6). 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’.

For laboratory data and physical examination, baseline will be defined as the latest non-missing assessment prior to first dose (Visit 6).

Absolute change from baseline outcome variables is computed as (post-randomization value – baseline value).

Percent change from baseline is computed as (post-randomization value – baseline value) / baseline value) × 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.

8.4.1.2 Visit and period windows

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

For non daily patient reported questionnaires collected in the ePRO, the variables will be summarized based on the protocol scheduled Days with ± 3-day window.

For the other questionnaires, the window is the same as the protocol-defined visit windows. For local laboratory data, and all vital signs, the visit recorded in the WBDC system will be used.

For the central laboratory results and other endpoints that present visit-based data, the variables will be summarized based on the scheduled days with adjusted analysis-defined visit windows.

A more detailed definition of visit and period windows will be provided in the statistical analysis plan.

8.4.2 Calculation or derivation of efficacy variables

8.4.2.1 Percentage reduction from baseline in prescribed oral corticosteroid dose

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

*{(Baseline dose–final dose)/baseline dose}*100%*

From week 32 - 40, the subjects should be on a maintenance dose of OCS and no reduction will be attempted. If a subject's asthma deteriorates during that time to the point that the subject requires an increase in the daily dose of OCS, that increased dose will be recorded in the CRF and deemed as the subject's final dose for analysis purposes, even if the increased dose is only taken after the 40 week treatment period.

If a subject discontinues from the study during the dose reduction period, 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 because the subject had not completed the period in which 5mg was used. In the event that 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 has prematurely discontinued IP, agreed to modified follow-up (Section 3.9.1) and data is not sufficient to verify asthma control 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 control could be verified.

Also, should a subject be placed on an every other day regimen of OCS, their final dose will be defined as the average daily dose. For example, if a subject is placed on a regimen of 2.5mg every other day, their final dose is defined as 1.25mg/day.

The impact of different imputation strategies for the final OCS dose will be explored.

8.4.2.2 The proportion of subjects with average final prescribed OCS dose ≤5.0 mg daily

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

Number of subjects with average final OCS dose ≤ 5 mg daily at final visit / number of subjects in treatment group

Final OCS is defined as in 8.4.2.1.

8.4.2.3 Proportion of subjects with ≥50% reduction from baseline in the prescribed oral corticosteroid dose

For an individual subject, if the calculation in section 8.4.2.1 results in a value of 50% or greater, that subject will be classified as having at least a 50% reduction in daily OCS dose. The proportion of such subjects will be calculated for each treatment group as:

Number of subjects with ≥50% reduction at final visit/number of subjects in treatment group

8.4.2.4 Area under the prescribed oral corticosteroid dose curve

Area under the OCS dose curve will be calculated using the time period from baseline to week 40. If a subject is discontinued from the study, the final dose as defined in 8.4.2.1 will be used for the time from discontinuation to week 40.

8.4.2.5 Proportion of subjects in different categories of reduction from baseline in oral prescribed corticosteroid dose

The percent reduction defined in Section 8.4.2.1 will be categorized into the following categories:

- 100% reduction (no OCS)
- ≥ 90% to < 100% reduction
- ≥ 75% to < 90% reduction
- ≥ 50% to < 75% reduction
- > 0 to < 50% reduction
- no change in average OCS dose
- increased average OCS dose

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

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

8.4.2.6 Proportion of subjects with ≥25% reduction from baseline and with average final OCS dose ≤5.0 mg daily

For an individual subject, if the calculation in section 8.4.2.1 results in a value of 25% or greater and if the average final OCS dose ≤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 ≥25% reduction from baseline and average final OCS dose ≤5.0 mg daily / number of subjects in treatment group

Final OCS dose is defined as in 8.4.2.1.

8.4.2.7 Proportion of subjects with ≤5.0 mg reduction from baseline in oral corticosteroid dose

For each treatment group, the number of subjects with change in average daily OCS dose ≤5.0 mg will be calculated. The proportion of such subjects will be calculated for each treatment group as:

Number of subjects with ≤5.0mg reduction at final visit / number of subjects in treatment group

Final OCS dose is defined as in 8.4.2.1.

8.4.2.8 Exacerbation rate

In the statistical analysis, the number of asthma exacerbations experienced by a subject during the 40-week double-blind treatment period will be used as response variable, and the logarithm of the subject's corresponding follow-up time will be used as an offset in the analysis to adjust for subjects having different exposure times during which the events occur. Asthma exacerbation is defined in Section 5.1.3.

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

Additional systemic corticosteroid treatments, ER or urgent care visits requiring use of systemic corticosteroids, or inpatient hospitalization due to asthma occurring during an exacerbation should 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.

Maximum 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.

For the production of summary statistics, the annual asthma 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 / (Follow-up date – Visit 6 date + 1).*

8.4.2.9 Time to first exacerbation

Time from randomization to the first asthma exacerbation 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 double-blind treatment period, or at the time point after which an exacerbation could not be assessed.

8.4.2.10 Proportion of subjects with ≥ 1 asthma exacerbation during 40 weeks of treatment

The proportion of subjects with ≥ 1 asthma exacerbation during the 40 weeks of treatment will be a supportive variable. The variable will categorize each subject as having at least one asthma exacerbation or not (yes/no).

8.4.2.11 Annualised asthma exacerbation rate associated with an ER or urgent care visit or a hospitalization

The number of asthma exacerbations that are associated with an ER or urgent care visit or a hospitalization experienced by a subject during the 40-week treatment period will be derived according to the following rule:

The start date of an asthma-related ER or urgent care visit or hospitalizations is the start date of the ER visit or urgent care or hospitalization.

The cessation date of an asthma-related ER or urgent care visit or hospitalization is the stop date of the ER visit or urgent care or hospitalization.

In the statistical analysis, the number of asthma exacerbations that are associated with an ER or urgent care visit or a hospitalization experienced by a subject during the 40-week double-blind treatment period will be used as response variable, and the logarithm of the subject's corresponding follow-up time will be used as an offset in the analysis to adjust for subjects having different exposure times during which the events occur.

Maximum follow-up time is approximately 40 weeks, and the follow-up time is derived as described in Section 8.4.2.5

Additionally, for the production of descriptive statistics, the annualised rate of asthma-related ER or urgent care visits and hospitalizations will be calculated using the same methodology as the annualised rate of exacerbations described in Section 8.4.2.5.

8.4.2.12 Lung Function Variables

FEV1, FVC and $FEF_{25-75\%}$ variables will be calculated based on the pre BD and the post BD measurements.

Percent change and absolute change from baseline (supportive variable) will be calculated as described in 8.4.1.1.

8.4.2.13 Diary Based Variables

For asthma symptom score, rescue medication use and home PEF, biweekly means will be calculated. A biweekly 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'.

Percent change from baseline will be calculated as described in 8.4.2.1.

Mean daily 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, night-time score, and total score will be calculated separately.

The total daily symptom score will be calculated by taking the sum of the daytime and night-time asthma symptom scores for each day. If a subject is missing a value for either daytime or night-time 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 biweekly mean daily asthma symptom total score.

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.

The number of inhalations of rescue medication captured in the eDiary each day will be calculated per subject. If a subject is missing a value for either morning or evening rescue medication on a given day, then the total rescue medication use for that day will be set to missing.

Total rescue medication use, defined as the average number of inhalations (puffs) per day will be calculated as the outcome variable.

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].

Biweekly mean number of inhalations (puffs) per day will be calculated as the outcome variable.

Nights with awakening due to asthma

The total biweekly percentage of nights with awakening due to asthma that required rescue medication will be calculated as the outcome variable.

Home peak expiratory flow (morning and evening)

Biweekly mean absolute changes from baseline in morning and evening PEF will be calculated.

8.4.2.14 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 BD. The questionnaire includes 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 main outcome variable for the ACQ-6 will be the ACQ-6 score, computed as the un-weighted mean of the responses.

Other variables based on ACQ-6 to report include:

- ACQ-6-responder (Yes=1/No=0)
  - Responder: Change from baseline ACQ-6 score ≤ -0.5
  - Non-responder : Change from baseline ACQ-6 score > -0.5
- ACQ-6-responder (improved/No Change / Deterioration)
  - Improvement: Change from baseline ACQ-6 score ≤ -0.5
  - No change: -0.5 < Change from baseline ACQ-6 score < 0.5
  - Deterioration: Change from baseline ACQ-6 score ≥ 0.5
- Subjects asthma control as measured by ACQ-6 score:

- Well controlled : ACQ-6 score ≤ 0.75
- Partly controlled : 0.75 < ACQ-6 score < 1.5
- Not well controlled : ACQ-6 score ≥ 1.5

8.4.2.15 Asthma Quality of Life Questionnaire for 12 Years and Older

Using the AQLQ(S)+12 questionnaire, 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).

The overall score is calculated as the mean response 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 main outcome variable for the AQLQ(S)+12 will be the change in mean overall score from baseline to each of the post-randomization periods. The change from baseline will be derived as post-randomization score minus baseline score, there will be no imputation for missing values.

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

- AQLQ(S) +12 -responder (Yes=1/No=0)
  - Responder: Change from baseline AQLQ(S) +12 score ≥ 0.5
  - Non-responder : Change from baseline AQLQ(S) +12 score < 0.5
- AQLQ(S) +12 -responder (improved/No Change / Deterioration)
  - Improvement: Change from baseline AQLQ(S) +12 score ≥ 0.5
  - No change: -0.5 < Change from baseline AQLQ(S) +12 score < 0.5
  - Deterioration: Change from baseline AQLQ(S) +12 score ≤ -0.5
- Change in mean domain score from baseline to each of the post-randomization periods

8.4.2.16 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 by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, 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 visual analogue scale will be calculated by visit as described in 8.4.1.1.

8.4.2.17 Health care resource utilization

Broad-based health care utilization event information will be collected by the Investigator/authorized delegate at each visit as specified in the protocol and recorded in the appropriate eCRF module. Examples include aspects such as unscheduled physician visits or telephone calls or ambulance transport.

8.4.2.18 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.

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 the work related questions, the following calculations should be used to create the outcomes of interest:

- Absenteeism = Q2/(Q2+Q4)
- Presenteeism = Q5/10
- Work Productivity Loss = Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)]
- Activity Impairment = Q10/10

The class related questions will be used in a similar manner.

8.4.3 Calculation or derivation of safety variable(s)

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

Change from baseline (Visit 6) to each post-baseline time point where scheduled assessments were made will be calculated for relevant measurements.

8.4.3.1 Adverse events

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

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

- AEs occurring during **run-in** (onset date ≥ Visit 1 and before the first dose of study treatment)
- AEs occurring **during treatment** (onset date ≥ the first day of study treatment and ≤ the last day of study treatment + *2 weeks*)
- AEs occurring during **follow-up**
    - (onset date > the last day of study treatment + *2 weeks* and ≤ week 54; *this is only applicable for subjects that are treated the entire treatment period*)
    - (onset date > the last day of study treatment + *2 weeks* and ≤ the last day of study treatment + 14 weeks; *this is only applicable for subjects that prematurely discontinued treatment*)
- AEs occurring **post-treatment** (onset date > the last day of study treatment + 14 weeks; *this is only applicable for subjects that prematurely discontinued treatment*)

The timing of AEs will be assigned to the period in which they first occurred. If an AE has a missing onset date, then unless the stop date of the AE indicates otherwise, this will be considered an on treatment event. Similarly, if an AE has a partial onset date, then unless the

partial onset date or the stop date indicates otherwise, this will be considered an on treatment AE.

8.4.3.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or discontinuations due to AEs.

Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that led to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

8.4.3.3 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, and will be assessed in a central laboratory. The parameters outlined in Table 5, Table 6, Table 7 and Table 8 in Section 5.1.6.1, will be collected. Laboratory data will be reported in SI units.

Changes in haematology and clinical chemistry variables between baseline and each subsequent scheduled assessment will be calculated. Baseline will be defined as the last available value measured prior to the first dose of randomized treatment. The change from baseline will be defined as the treatment period value minus the baseline period value. There will be no imputation for missing values.

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

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

For the purposes of haematology, clinical chemistry and urinalysis shift tables, baseline will be defined as the latest non-missing assessment prior to first dose, and on-treatment will be defined as the latest non-missing assessment whilst the subject is ongoing on treatment.

For the liver function tests: AST, ALT, ALP, GGT and total bilirubin, the multiple of the AstraZeneca ULN (not extended) 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:

- AST ≥ 3x ULN
- ALT ≥ 3x ULN
- TBL ≥ 2xULN

8.4.3.4 dECGs

Twelve-lead dECG measurements will be recorded in accordance with the protocol, with the baseline visit being defined as Visit 1.

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.

8.4.3.5 Physical Examination

Complete and brief physical examinations will be performed at time points specified in Table 1 and Table 2. What is included in the assessment will be dependent on whether the examination is complete or brief, as described in Section 5.1.7. For the brief physical examination, only information on whether the assessment was performed or not will be recorded.

Each component of the baseline visit (i.e., Visit 6) complete physical examination will be recorded as normal or abnormal. Each component of the follow-up complete physical examinations will be recorded as normal, same as baseline, or new/aggravated.

Any new finding(s), or aggravated existing finding(s) after Visit 1, judged as clinically significant by the Investigator, will be reported as an AE, as described in Section 6.1.

8.4.3.6 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 and Table 2.

Changes in vital signs variables between baseline and each subsequent scheduled assessment will be calculated. Baseline will be defined as the last value prior to the first dose of randomized treatment. The change from baseline will be defined as the treatment period value minus the baseline period value. There will be no imputation for missing values.

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

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

$$\mathbf{BMI = kg/m^2}$$

8.4.4 Calculations or derivation of Pharmacokinetic and Immunogenicity variables

Blood samples (processed to serum) for pharmacokinetic and immunogenicity assessments will be collected from all subjects at baseline prior to first tralokinumab administration at Visit 6, at multiple time points before tralokinumab administrations during the treatment period, and at selected time points 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 nAb activity. Both ADA and nAb will be summarized using descriptive statistics as described in Section 8.5.10.

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.

The incidence rate of ADA to tralokinumab will be reported by tralokinumab treatment group. If possible and if relevant, the impact of ADA occurrence on the PK and PD and safety will be summarized in the CSR.

8.5 Methods for statistical analyses

The main focus for the statistical analyses is to compare tralokinumab to placebo in with regards to primary, secondary, and safety objectives.

The analysis of the study endpoints will include all data captured during the 40-week double-blind treatment period. This includes data regardless of whether study treatment was prematurely discontinued or delayed, and/or irrespective of protocol adherence, unless the subject withdraws consent or assent to study participation. The statistical analyses will compare tralokinumab to placebo.

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. Variables will be summarized by visit, if applicable. All data will be listed. Data listings will be sorted by treatment, subject number.

All hypothesis testing will be reported using 2-sided tests. P-values will be rounded to 3 decimal places.

8.5.1 Testing strategy for primary and key 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:

The difference in the proportion of subjects with final OCS dose ≤5 mg will only be tested if the p-value for the test of difference in percentage reduction in OCS is less than 0.05.

The difference in the proportion of subjects with ≥50% reduction will only be tested if both p-values for the tests of difference in percentage reduction in OCS and difference in the proportion of subjects with final OCS dose ≤5 are less than 0.05.

No adjustments will be made for tests of safety or exploratory efficacy variables. Any results reported for these variables will be considered nominal (ie, unadjusted).

8.5.2 Sensitivity analyses

The interpretation data post-discontinuation of treatment is likely to be confounded by reduced quality of objective confirmation of deterioration, and by the use of subsequent therapies. Sensitivity analyses for the primary endpoint will be carried out to explore the impact of this, e.g. exclusion of data post-discontinuation of treatment or exclusion of data.

Also sensitivity analyses for the primary, secondary and supportive endpoints based on different missing data mechanism assumptions including those expected to be more conservative such as missing not at random will be used to explore the robustness of any treatment effect, including multiple imputation approaches.

Full details of the sensitivity analyses will be pre-specified in SAP and documented prior to database lock of the studies.

8.5.3 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 study treatment, didn't receive study treatment (and reason), completed treatment, discontinued treatment (and reason), completed study, and discontinued study (including reason).

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

Various baseline characteristics will also be summarized by treatment for the full analysis set. These include medical, surgical and respiratory disease histories, weight, height and BMI, smoking status, history of allergy, OCS dose at baseline, FEV_1 (pre and post-BD) at baseline, asthma duration, age at onset of asthma, asthma medications, the number of asthma exacerbations in the previous 12 months, and the number of asthma exacerbations requiring hospitalizations in the previous 12 months.

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

The number and percentage of subjects who take concomitant medications, and those who take disallowed concomitant medications during the study, will be presented by treatment group. Concomitant medications will be classified according to the AstraZeneca Drug Dictionary. The summary tables will present data by generic term using Anatomical Therapeutic Chemical (ATC) classification system codes.

8.5.4 Exposure

Exposure to IP will be summarized by treatment group, for the safety analysis set.

8.5.5 Violations and deviations

Only important protocol deviations will be listed and tabulated in the CSR. 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 (for any reason, unless otherwise specified) during the 40-week double-blind treatment period
- Subjects who received the incorrect study treatment or study dose at any time during the 40-week double-blind treatment period
- Subjects who developed withdrawal criteria during the study but were not withdrawn

8.5.6 Analysis of the primary variable

The primary efficacy variable is the percentage reduction from baseline in the subject's prescribed, OCS dose.

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

H_0: *difference in % reduction OCS dose (tralokinumab vs. Placebo)=0*

H_a: *difference in % reduction OCS dose (tralokinumab vs. Placebo)≠0*

The percentage reduction in OCS dose in tralokinumab treatment group will be compared to the percentage reduction in OCS dose in the placebo group using an analysis of covariance (ANCOVA) model.

The response variable in the model is the percentage reduction in OCS dose from baseline to 2 weeks after the final dose that the subject is receiving (Week 40, Visit 26). The model will include covariates of treatment group, age group and baseline OCS dose.

The estimated treatment effect (ie, difference in mean percentage reduction of tralokinumab versus placebo), corresponding 95% confidence interval (CI), and two-sided p-value for the difference will be presented. In addition, the percentage reduction in OCS and the corresponding 95% CI within each treatment group will be presented.

Due to the discrete nature of data, blinded data will be used to assess whether an analysis of covariance model is robust against the departure from the assumption of normal data. Any changes of the primary analysis based on this assessment will be documented in the SAP.

8.5.7 Analysis of secondary variable(s)

8.5.7.1 The proportion of subjects with average final prescribed OCS dose ≤5.0 mg daily

The proportion in the tralokinumab group will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for age group and baseline OCS dose.

The results of the analyses will be presented as difference in the proportion of subjects reaching ≤ 5mg daily, together with associated 95% CI and 2-sided p-value. The number and percentage of subjects reaching ≤ 5mg daily will also be summarized by randomized treatment.

8.5.7.2 Proportion of subjects with ≥50% reduction from baseline in prescribed oral corticosteroid dose

The proportion of subjects with ≥50% will be summarized and analyzed using the approach defined for the proportion of subjects with average final prescribed OCS dose ≤5.0 mg daily, as described in Section 8.5.7.1.

8.5.8 Analysis of supportive and exploratory variables

8.5.8.1 Area under the in prescribed oral corticosteroid dose curve

The area under the 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 8.5.6.

8.5.8.2 Proportion of subjects in different categories of reduction from baseline in oral corticosteroid dose

To support the primary analysis the reduction in baseline OCS will be evaluated descriptively using the categorical variable defined in Section 8.4.2.5.

The results of the analyses will be presented as differences versus placebo in the proportion of subjects in each group, together with the associated 95% CI.

8.5.8.3 Proportion of subjects with ≥25% reduction from baseline and with average final prescribed OCS dose ≤5.0 mg daily

Proportion of subjects with ≥25% reduction from baseline and with average final OCS dose ≤5.0 mg daily with 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 average final prescribed OCS dose ≤5.0 mg daily, as described in Section 8.5.7.1.

8.5.8.4 Proportion of subjects with ≤5.0 mg reduction from baseline in oral corticosteroid dose

The proportion of subjects with ≤5.0 mg reduction from baseline in average daily oral corticosteroid 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 average final prescribed OCS dose ≤5.0 mg daily, as described in Section 8.5.7.1.

8.5.8.5 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 double-blind treatment period. Covariates and factors included in the model will include at least treatment and the stratifying variables. The logarithm of the subject's corresponding follow-up time will be used as an offset variable in the model to adjust for subjects having different exposure times during which the events occur.

The standard parameterization approach (NB2) of the Negative Binomial model will be applied (Hilbe 2011).

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

The individual exacerbation criteria (ER or urgent care visits due to asthma that required systemic corticosteroids, hospitalization due to asthma, or use of systemic corticosteroids) will also be summarized descriptively.

8.5.8.6 Other endpoint associated with asthma exacerbations

The proportion of subjects with ≥1 asthma exacerbation will be summarized and analyzed using the approach defined for proportion of subjects with ≥50% reduction, as described in Section 8.5.7.2.

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 with including treatment and at least stratifying variables as covariates.

Results of the analysis will be summarized as hazard ratios and 95% confidence intervals.

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.

8.5.8.7 Emergency room or urgent care visits and hospitalizations due to asthma

Annual rate of asthma exacerbations that are associated with an ER or urgent care visit or a hospitalization will be analyzed using a similar negative binomial model as outlined for the efficacy variable in Section 8.5.8.5.

8.5.8.8 Lung Function

The percent change from baseline in pre-BD FEV_1, FVC and $FEF_{25-75\%}$ at Week 12 and 40 will be compared between tralokinumab and placebo using a repeated measures analysis on all subjects with a baseline measurement in the full analysis set.

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). Treatment group and the variables used in the stratified randomization will be included as independent variables. Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is:

*Percent change in lung function variable= Treatment group + stratifying variables + visit + treatment*visit*

Results will be presented in terms of LSMEANS, treatment differences in LSMEANS and 95% confidence intervals.

8.5.8.9 Asthma symptoms

The change from baseline in asthma symptom total score, daytime score, and night-time score at Week 12 and 40 will each be summarized and analyzed using the repeated measurement approach defined for change from baseline in pre-BD FEV_1, as described in Section 8.5.8.8. Included in the model will also be the baseline mean daily asthma symptom score.

8.5.8.10 Asthma symptom, general health-related quality of life and asthma control

Rescue medication use

Total rescue medication use (average puffs/day) will be summarized and analyzed using a similar model as for the change from baseline in pre-BD FEV_1, as described in Section 8.5.8.8.

Home PEF (morning and evening)

Change from baseline in morning and evening PEF at Week 40 will each be summarized and analyzed using the same approach as for the change from baseline in pre dose/pre-BD FEV_1, as described in Section 8.5.8.8.

Nights with awakening due to asthma

The percentage of nights with awakening due to asthma and requiring rescue medication will be summarized and analyzed in the same way as rescue medication use, described above.

8.5.8.11 ACQ-6 defined asthma control

Change in mean score from baseline for ACQ-6 will be summarized and analyzed using the repeated measurement approach defined for change from baseline in pre-dose/pre-BD FEV_1, as described in Section 8.5.8.8. Included in the model will also be the baseline ACQ-6 mean score.

Responder variables ACQ-6 (yes/no) at Week 12 and Week 40 will be analyzed using a logistic regression model with covariates of at least treatment, stratifying variables, and baseline value.

The number and percentage of subjects achieving mean ACQ-6 ≤ 0.75, $0.75 <$ mean ACQ-6 <1.5 and mean ACQ-6 of ≥ 1.5 at EOT will be summarized by treatment. Additionally, the number and percentage of subjects achieving an improvement, no change, or deterioration as per Section 8.4.2.14, ACQ-6 will also be summarized by treatment.

Supportive outcome measure: change from baseline to overall post-baseline mean of ACQ-6.

8.5.8.12 Asthma specific health-related quality of life

The change in mean score from baseline for AQLQ(S)+12 at Week 12 and 40 will be summarized and analyzed using the repeated measurement approach defined for change from baseline in pre-dose/pre-BD FEV_1, as described in Section 8.5.8.8. Included in the model will also be the baseline AQLQ(s)+12 total score.

Responder variables AQLQ(S)+12 (yes/no) at Week 12 and 40 will be analyzed using a logistic regression model with covariates of at least treatment, stratifying variables, and baseline value.

The number and percentage of subjects with AQLQ(s)+12 total score changes ≥ 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 8.4.2.5.

Supportive outcome measure: change from baseline to overall post-baseline mean of AQLQ(S)+12.

8.5.8.13 European quality of life-5 dimensions-5 levels (EQ-5D-5L)

The EQ-5D-5L responses from each dimension and the visual analogue scale (VAS) will be summarized by treatment group and period. Shift tables will be produced for each dimension, and the change from baseline in VAS will be summarized with descriptive statistics by visit.

8.5.8.14 Health care resource utilization and productivity loss due to asthma

WPAI-CIQ

The WPAI+CIQ data will be summarized by treatment, including the 4 types of scores: absenteeism, presenteeism, work/class productivity loss, and activity impairment described. The number and percentage of subjects with asthma specific resource utilization (defined in Section 8.4.2.18) will be presented by treatment group.

8.5.9 Safety and tolerability

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

8.5.9.1 Adverse events

AEs will be summarized separately for the treatment and follow-up periods, as defined in Section 6.3. AEs occurring during the run-in period, or occurring post-treatment (as per the definition above) 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, SAEs, deaths due to AE, discontinuation if IP due to AEs (DAEs), and other significant adverse events (OAEs). The total number of AEs in the different AE categories in terms of AE counts will also be presented (ie, accounting for multiple occurrences of the same event in a subject).

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

AEs (by PT) will be summarized by causality and maximum intensity. If a subject reports multiple occurrences of the same AE, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe). SAEs, OAEs, DAEs, and deaths will also be summarized in separate tables.

The rate of AEs per person-years at risk, calculated as (number of subjects reporting AE)/(total time at risk of AE), will also be reported. Rates will typically be expressed in terms of events per 100 subject-years.

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

8.5.9.2 Laboratory data

All continuous laboratory parameters will be summarized by absolute value at each visit by treatment group, together with the corresponding changes from baseline, in both primary populations. 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.

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

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

Data for subjects who have treatment-emergent changes outside the predefined criteria will be presented. This data presentation will include all visits for this subset of subjects.

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

In order to identify potential Hy's Law cases, maximum post baseline total bilirubin will be plotted against maximum post baseline ALT, expressed as multiples of ULN. This plot will be repeated to show maximum post baseline total bilirubin 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 total bilirubin and at 3xULN for ALT/AST.

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

For urinalysis data, a shift table will be generated to present changes from baseline to EOT. The number of subjects with treatment-emergent changes will also be summarized. Here, treatment-emergent changes are defined as None/Trace at baseline to Positive, at any visit after baseline.

Any data outside the AstraZeneca normal and extended reference ranges will be explicitly noted on the listings that are produced.

8.5.9.3 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.

8.5.9.4 Physical Examination

Shift tables (normal, abnormal) of baseline versus EOT will be generated, presenting the assessment for each component of the complete physical examination separately.

Listings of abnormal results will be produced.

8.5.9.5 Vital Signs

Vital signs data will be presented in the same way as described in Section 8.4.3.3 for the clinical laboratory data, and will be presented using AstraZeneca defined reference ranges, and clinically important change criteria.

All recorded vital signs data will be listed.

8.5.9.6 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, standard deviation, 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 (positive vs. negative) will also be classified and summarized by treatment group. The association of ADA status across the study (positive vs. negative) with AEs/SAEs may be evaluated. 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 positive ADA for any visit during the study. Otherwise, the subject will be considered as ADA negative. The associations between ADA and AE/SAEs may be summarized for positive. The ADA-positive subjects 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. 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 antibody evaluations will be conducted on those serum samples that test positive for ADA at end of treatment and also during the study follow up period. 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. Samples positive for nAb to tralokinumab are then titered to determine relative amounts of nAb present in each test sample.

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

8.5.10 Analysis of pharmacokinetics

All analyses of pharmacokinetics variables will be based on the PK data set. All analyses on immunogenicity variables will be based on the safety analysis set.

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

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

8.5.11 Interim analysis

No interim analysis is planned for this study.

8.5.12 Exploratory analysis

The analysis of exploratory objectives will be specified in the statistical analysis plan.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational site staff, and also train them on any study specific procedures, the WBDC and IVR/IWR systems, ePRO and ePEF devices, spirometers, and any other system(s) that may be utilised in the study.

The Principal Investigator will ensure that appropriate training relevant to the study is provided to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will ensure that a record of all individuals involved in the study (medical, nursing and other staff) is maintained.

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contact with the study site, including site visits to:

Provide information and support to the Investigator(s)

Confirm that facilities remain acceptable

Confirm that the investigational site team is adhering to the protocol, data are being accurately and timely recorded in the CRFs, biological samples are handled in accordance with the Laboratory Manual, and that study drug accountability checks are being performed

Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent or assent of participating subjects. This will require direct access to all original records for each subject (eg, clinic/hospital charts)

Ensure withdrawal of informed consent or assent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the Investigator(s) or other personnel at the site require information and advice about the study conduct.

9.2.1 Source data

Please refer to the Clinical Study Agreement (CSA) for location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the site should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects. In all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The Investigator should follow the principles and terms outlined in the CSA pertaining to the archival of study documents.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study is expected to start in Q1, 2015 and to end by Q4, 2017.

The study may be terminated at individual sites if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with tralokinumab.

9.4 Data management by AstraZeneca

Data management will be performed by the AstraZeneca Data Management Centre according to the Data Management Plan (DMP). Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The DMP will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

Data will be entered in the WBDC system at the study site.

Site personnel will be trained on use of the WBDC system and will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system. eCRF Instructions will be provided to the personnel at the study site as guidance for performing data entry. Data entered in the WBDC system will be immediately saved to a central database and all changes will tracked in the system's audit trail. All data will be Source Data Verified (SDV) by an AstraZeneca site monitor (or representative), reviewed /queried and updated as needed.

Data queries will be raised for inconsistent, impossible, or missing data, and must be resolved in a timely manner. Clean file occurs when all data have been declared clean and signed off by all Investigators. Data will be frozen and then locked to prevent further data entry/editing. Any treatment revealing data may thereafter be added and the final database will be locked. A copy of the eCRFs will be provided to and archived at the study site when the study has been locked.

Data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports will be produced and reconciled with the Subject Safety database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

Management of external data

Data Management will determine the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (as applicable).

Data Management will ensure that the data collection tool (eg, ePRO diary, IVRS/IWRS, etc) will be tested/validated as necessary. External data reconciliation will be done with the clinical database as applicable.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The Informed Consent or assent Form(s) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Ethics Committee (EC)/Institutional Review Board (IRB) should approve the final study protocol, including the final version of the subject's ICF (and assent form for subjects under the age of majority), and any other written information and/or materials to be provided to a subject. The Investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The EC/IRB should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the ICF (and/or assent form for subjects under the age of majority) that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the ICF (and assent form for subjects under the age of majority), should be approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, ECs/IRBs and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent and assent

The Principal Investigator(s) at each site will:

Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study

Ensure each subject is notified that they are free to discontinue from the study at any time

Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided

Ensure each subject provides signed and dated informed consent (and assent form for subjects under the age of majority) before conducting any procedure specifically for the study

Ensure the original, signed ICFs (and assent form for subjects under the age of majority) are stored in the Investigator's Study File

Ensure copies of the signed ICFs (and assent form for subjects under the age of majority) are given to the subject

Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent or assent form that is approved by an Ethics Committee.

10.5 Changes to the protocol and informed consent or assent forms

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator, and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant EC/IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to ECs/IRB, see Section 10.3.

If a protocol amendment requires a change to a site's ICF (and/or assent form for subjects under the age of majority), AstraZeneca and the site's EC/IRB are to approve the revised ICF (and/or assent form for subjects under the age of majority) before the revised form(s) is/are used.

If local regulations require, any administrative change will be communicated to or approved by each EC/IRB.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC/IRB may perform audits or inspections at the site, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the site.

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Clinical Study Protocol Appendix B	
Drug Substance	Tralokinumab
Study Code	D2210C00013
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Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix C

Drug Substance	Tralokinumab (CAT-354)
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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

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Clinical Study Protocol Appendix D

Drug Substance	Tralokinumab (CAT-354)
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Appendix D
Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

TABLE OF CONTENTS PAGE

1. INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Clinical Study Protocol Appendix E	
Drug Substance	Tralokinumab (CAT-354)
Study Code	D2210C00013
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Appendix E
Maintenance Therapy Equivalence Table

Estimated daily doses for inhaled corticosteroids.

Asthma Therapy	**Total Daily Dose (µg/day)**	
Inhaled Corticosteroid	**Medium**[1]	**High**
Beclomethasone dipropionate	>500 - **1000**	>1000 - 2000
Beclomethasone HFA	>240 - **480**	>480
Beclomethasone dipropionate (Fostair)	>200 - **400**	>400 - 800
Ciclesonide	>160 - **320**	>320 - 1280
Triamcinolone acetonide	>1000 - **2000**	>2000
Flunisolide	>1000 - **2000**	>2000
Fluticasone fuorate	**100**	200
Fluticasone propionate	>250 - **500**	>500 - 1000
Fluticasone propionate HFA	>364 - **440**	>440
Budesonide	>400 to **800**	>800 - 1600
Budesonide, if as delivered dose (eg Symbicort)	>320 to **640**	>640 - 1280
Mometasone furoate	**≥400**	≥800

[1] The acceptable medium ICS dose for this study is bolded.

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Clinical Study Protocol Appendix F	
Drug Substance	Tralokinumab (CAT-354)
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Appendix F
Anaphylaxis: definition criteria, signs and symptoms, and management

1. INTRODUCTION

As with any antibody, allergic reactions to dose administration are possible. The World Health Organization has categorized anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic [IgE-mediated and non-IgE-mediated (e.g., IgG and immune complex mediated) and nonimmunologic (Johansson et al, 2004). The clinical criteria for defining anaphylaxis for this study are listed in section 2. A guide to the signs and symptoms and management of acute anaphylaxis is provided in section 3. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognize and treat anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs, a blood sample will be drawn from the patient as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge for analysis of serum tryptase.

2. CLINICAL CRITERIA FOR DEFINING ANAPHYLAXIS AND IMMUNE COMPLEX DISEASE

Anaphylaxis

In adults, anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   (a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

   (b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   (a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

   (b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

(c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence).

(d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours): Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that patient's baseline.

Immune Complex Disease

Immune complex disease or Hypersensitivity Type III is evoked by the deposition of antigen-antibody or antigen-antibody-complement complexes on cell surfaces, with subsequent involvement of breakdown products of complement, platelets, and polymorphonuclear leukocytes, and development of vasculitis; serum sickness and nephritis is common.

3. SIGNS AND SYMPTOMS AND MANAGEMENT OF ACUTE ANAPHYLAXIS

Anaphylaxis is an acute and potentially lethal multi-system allergic reaction in which some or all of the following signs and symptoms occur:

- Diffuse erythema
- Pruritus
- Urticaria and/or angioedema
- Bronchospasm
- Laryngeal edema
- Hypotension
- Cardiac arrhythmias
- Feeling of impending doom
- Unconsciousness
- Shock

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles
- Rhinorrhea

- Change in voice

- Metallic taste

- Nausea, vomiting, diarrhea, abdominal cramps and bloating

- Lightheadedness

- Headache

- Uterine cramps

- Generalized warmth

4. MANAGEMENT OF ACUTE ANAPHYLAXIS

4.1 Immediate intervention

1. Assessment of airway, breathing, circulation, and adequacy of mentation
2. Administer epinephrine intramuscularly every 5-15 minutes, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms such as respiratory distress, hypotension, shock and unconsciousness.

4.2 Possibly appropriate, subsequent measures depending on response to epinephrine

(a) Place patient in recumbent position and elevate lower extremities.

(b) Establish and maintain airway.

(c) Administer oxygen.

(d) Establish venous access.

(e) Normal saline IV for fluid replacement.

4.3 Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion.

(b) Consider H1 and H2 antihistamines.

(c) Consider nebulized β2 agonist [e.g., albuterol (salbutamol)] for bronchospasm resistant to epinephrine.

(d) Consider systemic corticosteroids.

(e) Consider vasopressor (e.g. dopamine).

(f) Consider glucagon for patient taking b-blocker.

(g) Consider atropine for symptomatic bradycardia.

(h) Consider transportation to an emergency department or an intensive care facility.

(i) For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary.

Adapted from: Kemp SF, Lockey RF, Simons FE; World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy. 2008; 63(8):1061-70.

AstraZeneca

Clinical Study Protocol Appendix G	
Drug Substance	Tralokinumab (CAT-354)
Study Code	D2210C00013
Edition Number	3.0
Date	22 February 2016

Appendix G
Restricted and prohibited medications

PROHIBITED AND RESTRICTED MEDICATIONS

Asthma medication restrictions

Medication	Prohibited/restricted	Details
Maintenance treatment with long-acting bronchodilators (including ICS/LABA combinations)	Restricted	Changes in dose and regimen should not be done from enrolment and throughout the study treatment (unless there is a medical need as judged by the Investigator) Usual ICS/LABA should not be taken prior to scheduled spirometry, ECG and home lung function assessments (to be administered once assessments are completed) Subjects should be instructed not to use their twice daily bronchodilator within 12 hours of the scheduled site visit spirometry. For once daily bronchodilators a 48 hour washout period is required. Subjects will not need to washout of their asthma medications for unscheduled visits due to asthma worsening.
Short acting beta-agonists (SABA)	Restricted	Regular scheduled use not allowed from enrolment through the study duration. Rescue use of SABA administered via nebulization is discouraged, except as urgent treatment during an asthma exacerbation. SABA should not be used within 6 hours prior to scheduled site visit spirometry, ECG and home lung function assessments with the

		exception of any unscheduled visits due to asthma worsening, ECG and home lung function assessments.
Additional Maintenance Controllers	Allowed with restriction	Stable dose for 3 months prior to Visit 1; stable dose during the treatment period Subjects on theophylline should have blood concentration levels within therapeutic range documented before Visit 1. Subjects should be instructed not to use theophylline and additional once daily bronchodilators within 48 hours of the scheduled site visit spirometry at site visits with the exception of any unscheduled visits due to asthma worsening.
Short acting anticholinergics (e.g. ipratropium)	Restricted	Not allowed from enrollment and throughout the study as a rescue treatment for worsening asthma symptoms outside of managing an asthma exacerbation event May be used for managing an asthma exacerbation event.
Long-acting beta-agonists as a reliever (e.g. Symbicort Maintenance and Reliever Treatment)	Prohibited	Not allowed from enrolment and throughout the study duration
Zileuton	Prohibited	Not allowed 30 days prior to Visit 1;during treatment period

Other medication restrictions

Medication	**Prohibited/restricted**	**Details**
Live Attenuated Vaccines	Prohibited	Not allowed 30 days prior to the date of randomization; during treatment -

Medication	Prohibited/restricted	Details
		and follow-up period.
Inactive/killed vaccinations (e.g. inactive influenza)	Restricted	Allowed provided they are not administered within 5 days before or after any study visit
Any immunomodulators or immunosuppressives (other than prior, stable OCS for the maintenance treatment of asthma)	Prohibited	Not allowed 3 Months or 5 Half Lives (whichever is longer) prior to Visit 1; during treatment period; 3 Months or 5 Half Lives (whichever is longer) after Last Dose
Blood products or immunoglobulin therapy	Prohibited	Not allowed 30 days prior to date of ICF; during treatment period
Any marketed (eg omalizumab) or investigational biologic treatment	Prohibited	Not allowed 4 months or 5 half-lives (whichever is longer) prior to the date of randomization; during treatment period; 4 months or 5 half-lives (whichever is longer) after the last dose of the investigational product
Other investigational Products (including investigational use of an approved drug)	Prohibited	Not allowed 30 Days or 5 Half Lives (whichever is longer) prior to Visit 1; during treatment period
Allergen Immunotherapy	Restricted	Allowed if on stable therapy for at least 30 days prior to date of ICF; no anticipated changed during treatment period
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases	Prohibited	Not allowed 30 days prior to Visit 1;during treatment period
Roflumilast	Prohibited	Not allowed 30 days prior to Visit 1;during treatment period
Oral or ophthalmic non-selective β-adrenergic	Prohibited	Patients currently using any oral or ophthalmic non-selective β-adrenergic antagonist at the time of enrolment are

Medication	Prohibited/restricted	Details
antagonist (e.g. propranolol)		not eligible for the study. Not allowed during treatment period.
Medications not currently licensed for use in the treatment of asthma, for example medications approved for Chronic Obstructive Pulmonary Disease and not part of current standard of care	Prohibited	Not allowed 30 days prior to Visit 1; Not allowed throughout the duration of the study