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**Clinical Study Protocol**

Drug Substance	Tralokinumab (CAT-354)
Study Code	D2210C00029
Version	2.0
Date	15 June 2017

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**A 52-Week, Open-Label, Multicentre Study to Evaluate the Safety of Tralokinumab in Japanese Adults and Adolescents with Asthma Inadequately Controlled on Inhaled Corticosteroid plus Long-Acting  $\beta_2$ -Agonist**

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Sponsor: 





## VERSION HISTORY

<b>Version 1.0, 19 July 2016</b>
Initial Creation
<b>Version 2.0, 15 June 2017</b>
<p>Section 3.1 Inclusion criteria: Numbering was corrected only for Japanese version.</p> <p>Section 3.6 Discontinuation of investigational product 8 D): This section was updated to clarify the discontinuation criteria only for Japanese version.</p> <p>Section 4 Study plan and timing of procedures, Table 1 Study Plan: Table 1 was corrected to indicate that HbA1c is collected as Visit 3, which aligns with Table 4.</p> <p>Section 4.2 Treatment Period: This section was updated to clarify that if a subject selects Option 1, 2 or 3 at the IPD visit, no follow up visits are required. Additionally, text describing final follow up visit timing moved up in the section to improve flow of information related to visit timing.</p> <p>Section 7.7.1 Concomitant medications, Maintenance of asthma controller medication: To clarify ICS dose, text changed to indicate a dose of ICS is required prior to Visit 1, and this dose should be maintained at a stable dose from Visit 2 until the end of the treatment period.</p>

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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

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### **A 52-Week, Open-Label, Multicentre Study to Evaluate the Safety of Tralokinumab in Japanese Adults and Adolescents with Asthma Inadequately Controlled on Inhaled Corticosteroid plus Long-Acting $\beta_2$ -Agonist**

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#### **National Co-ordinating Investigator**

[REDACTED]  
[REDACTED]  
[REDACTED]

#### **Study site(s) and number of subjects planned**

Approximately 26 subjects will enter treatment at approximately 4 centres in Japan.

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<b>Study period</b>	<b>Phase of development</b>	
Estimated date of first subject enrolled	Q4 2016	3
Estimated date of last subject completed	Q2 2018	

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#### **Study design**

This is an open-label study designed to evaluate the safety of a fixed 300 mg dose every 2 weeks (Q2W) of tralokinumab administered subcutaneously in subjects with inadequately controlled asthma on medium to high-dose of inhaled corticosteroid plus long-acting  $\beta_2$ -agonist.

Approximately 26 Japanese subjects will be recruited into the study and receive tralokinumab in order to reach 22 completed.

All subjects will receive tralokinumab 300 mg every 2 weeks via subcutaneous injection at the study site, over a 52-week treatment period.

After the initial enrolment and confirmation of the entry criteria, subjects will proceed to a run-in period of maximum 2 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Subjects who meet the eligibility criteria will enter the 52-week treatment period. 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 treatment period.

Follow-up visits will be conducted at Weeks 56 and 66. The 14-week extended follow-up period is to ensure that adequate evaluation of immunogenicity can be determined.

## Objectives

Primary Objective:	Outcome Measure:
To assess the safety and tolerability of tralokinumab.	<ul style="list-style-type: none"> <li>• Adverse Events (AEs) and Serious Adverse Events (SAEs)</li> <li>• Laboratory variables</li> <li>• Physical examinations</li> <li>• Vital signs</li> <li>• ECG</li> </ul>

Exploratory Objective:	Outcome Measure:
To collect data for the assessment of efficacy of tralokinumab	<ul style="list-style-type: none"> <li>• Asthma Control Questionnaire-6 score (ACQ-6)</li> <li>• Forced expiratory volume in one second (FEV<sub>1</sub>)</li> </ul> <p><b>Key Outcome Variable:</b> Percent change from baseline in pre-dose/pre-BD-FEV<sub>1</sub></p> <ul style="list-style-type: none"> <li>• Asthma exacerbation</li> </ul> <p><b>Key Outcome Measure:</b> Annual asthma exacerbation rate</p>
To explore baseline level and change from baseline of biomarkers	<ul style="list-style-type: none"> <li>• Periostin</li> <li>• Dipeptidyl peptidase-4 (DPP-4)</li> <li>• Other biomarkers that may be associated with up-regulation of interleukin-13</li> </ul>
To evaluate the pharmacokinetics and immunogenicity of tralokinumab	<ul style="list-style-type: none"> <li>• Serum tralokinumab concentration</li> <li>• Incidence of positive assessments for anti-drug antibodies (ADA) and characterization of their neutralizing potential</li> </ul>

## Target subject population

Male and female adults and adolescents, 12 to 75 years of age inclusive, with asthma inadequately controlled by treatment with inhaled corticosteroid plus long-acting  $\beta_2$  agonist treatment.

## Duration of treatment

Following an initial enrolment at Week -2, subjects will enter a maximum 2-week run-in period which will be followed by a 52-week treatment period. The first dose of tralokinumab

will be administered at Week 0. Subsequent doses will be administered every 2 weeks up until Week 50 (for a total of 26 doses) with an end of treatment visit occurring at Week 52. Post treatment safety follow up visits will be performed at Weeks 56 and 66.

**Investigational product, dosage and mode of administration**

Tralokinumab 300 mg (150 mg/mL), will be administered to subjects at the site via subcutaneous injection using 2 pre-filled syringes each containing 1 ml.

**Statistical methods**

No formal sample size calculation was conducted for this study. Approximately 22 Japanese patients who complete the planned 52-weeks treatment period are considered appropriate for collecting additional safety information of tralokinumab (300 mg SC Q2W) among Japanese patients. With an assumed drop-out rate of 15% during the 52-weeks treatment period, approximately 26 Japanese patients are needed to be dosed.

The interim and final analyses of the study are primarily descriptive using descriptive statistics. Where appropriate, an exact 95% confidence interval will be calculated. No hypothesis testing will be conducted for this study.

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

<b>Abbreviation or special term</b>	<b>Explanation</b>
ACQ-6	Asthma Control Questionnaire-6
ADA	Anti-Drug Antibodies
AE	Adverse event
AAER	Annual Asthma Exacerbation Rate
ALP	Alkaline Phosphate
ALT	Alanine Aminotransferase
APFS	Accessorized Prefilled Syringe
AST	Asparate Aminotransferase
BD	Bronchodilator
B-HCG	Beta-Human Chorionic Gonadotropin
BUN	Blood Urea Nitrogen
CO <sub>2</sub>	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form (electronic/paper)
CRP	C-Reactive Protein
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DAE	Discontinuation of Investigational Product due to Adverse Event
DPP-4	Dipeptidyl Peptidase-4
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ED	Emergency Department
ER	Emergency Room
EOT	End of Treatment
FEF 25-75%	Forced Expiratory Flow at 25-75% of the forced vital capacity

<b>Abbreviation or special term</b>	<b>Explanation</b>
FEV <sub>1</sub>	Forced Expiratory Volume in 1 second
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice Unless otherwise noted, 'GCP' shall mean 'the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice' (ICH GCP) and the Japanese 'Good Clinical Practice for Trials on Drugs (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications' (GCP Ordinance).
GGT	Gamma-Glutamyl Transpeptidase
GINA	Global Initiative for Asthma
GLI	The Global Lung Function Initiative
GMP	Good Manufacturing Practice
HbA1c	Glycosylated haemoglobin
HIV	Human Immunodeficiency Virus
IATA	International Air Transport Association
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroids
IgE	Immunoglobulin E
IL	Interleukin
IL-13	Interleukin-13
IP	Investigational Product
IPD	Investigational Product Discontinuation
IRB	Investigational Review Board
ISF	Investigator Study File
ITT	Intent-to-Treat
IUO	Investigator Use Only
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JRS	Japanese Respiratory Society
LABA	Long-Acting $\beta_2$ -Agonist
LSLV	Last Subject Last Visit
LTRA	Leukotriene Receptor Antagonists

<b>Abbreviation or special term</b>	<b>Explanation</b>
MAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralizing Antibodies
OAE	Other Significant Adverse Event
OCS	Oral Corticosteroids
PD	Pharmacodynamic(s)
PEF	Peak Expiratory Flow
PEO	Performance Evaluation Only
PI	Principal Investigator
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PNV	Predicted Normal Value
PRO	Patient Reported Outcome
PT	Preferred Term
Q2W	Every 2 Weeks
SABA	Short-Acting $\beta_2$ -Agonist
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
Th2	T Helper 2 Cells
TBL	Total Bilirubin
TLC	Total Lung Capacity
ULN	Upper Limit of Normal
UNS	Unscheduled
WBDC	Web Based Data Capture
WOCBP	Women of Childbearing Potential

## 1. INTRODUCTION

### 1.1 Background and rationale for conducting this study

Asthma is a syndrome characterized by airway inflammation, reversible airway obstruction and airway hyper-responsiveness, with a global prevalence of approximately 300 million patients (GINA 2016).

Approximately 5% to 10% of asthma patients have severe asthma, many of whom may be inadequately controlled by inhaled corticosteroids (ICS) and long-acting  $\beta_2$ -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 hyper-responsiveness (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<sub>1</sub>)), 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 effects in FEV<sub>1</sub> that were greater than that observed with a 150 mg dose (Piper et al 2013). Since low pre-bronchodilator (BD) FEV<sub>1</sub> 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 in this population (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 the 2 regimens (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 phase 2b population, an increase from baseline in pre BD FEV<sub>1</sub> to the end of treatment was seen with the Q2W dosing regime, but not with the Q2/4W dosing regime. In this phase 2b



study, a subpopulation reversible on entry ( $FEV_1$  reversibility  $\geq 12\%$  and  $\geq 200$ ml in  $FEV_1$ ) an AAER reduction that was greater for the tralokinumab 300 mg Q2W cohort versus the Q2/4W cohort was seen. A further reduction of AAER was observed in a subgroup of reversible subjects with high ( $>$  median) serum periostin, a biomarker induced by IL-13 (Brightling et al 2015). This is the population which is studied in the ongoing pivotal studies in severe asthma studied in phase 3. The safety profile of all doses studied so far has been acceptable (for further details see the investigators brochure (IB)).

The purpose of this long term safety study is to provide additional safety data of tralokinumab in the treatment of Japanese subjects with severe uncontrolled asthma despite treatment with ICS-LABA and any other additional controller medication. The study will evaluate the safety of Tralokinumab with regards to adverse events, physical examination as well as other safety parameters.

The main reason for this study is to provide additional safety data in Japanese patients. This need for additional safety is mainly driven by lower than expected recruitment of Japanese patients in the Pivotal phase 3 program. Additional Japanese patients are expected to be sufficient.

## 1.2 Rationale for study design and doses

This is an open-label un-controlled study designed to evaluate the safety and tolerability of a fixed dose of tralokinumab (300 mg) administered via SC injection every 2 weeks throughout a 52-week treatment period. Exacerbation-prone asthma subjects who remain uncontrolled on ICS-LABA, and who demonstrate a pre-bronchodilator (pre-BD)  $FEV_1$  of  $\geq 40\%$  predicted at either Visit 1 (enrolment/run-in) or Visit 2 (treatment), will be registered into the study.

Previous efficacy studies of tralokinumab, including a phase 2b study with subjects on high dose ICS-LABA with or without additional asthma controller medications, have been conducted in adult subjects (18-75 years of age), and provide the basis for this long term safety study. Pharmacokinetic 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. Adolescent subjects are therefore to be included as part of the study population.

Analysis of data from both phase 2 studies, MI-CP199 and 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 MI-CP199) 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. Since the safety profile in the CD-RI-CAT-354-1049 study was acceptable in both treatment cohorts, and no clear safety related dose-response pattern was identified, the dose of 300 mg Q2W has been selected for evaluation in this long term safety study.

Pharmacokinetic/pharmacodynamic (PK/PD) modelling using all data obtained to date has also confirmed that a dose of 300 mg Q2W will result in near maximal increase in pre-BD FEV<sub>1</sub> in the phase 3 subject population.

Subjects will receive maintenance therapy that includes their usual dose of ICS- LABA and additional asthma controllers (see section 7.7.2).

### 1.3 Benefit/risk and ethical assessment

There are few treatment options for subjects whose asthma remains uncontrolled on ICS-LABA (GINA 2016). The evidence base for oral add-on therapies (i.e. oral corticosteroids (OCS), leukotriene inhibitors (LTRAs), and xanthenes) is limited. Anti-immunoglobulin E (IgE) therapy (i.e., 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. Thus, in a 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 program) provided improvement of lung function (FEV<sub>1</sub>), 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 this study, tralokinumab at a fixed dose of ≥ 300 mg SC every other week produced improvements in multiple metrics of asthma control, including the annualised asthma exacerbation rate (AAER), lung function, ACQ-6 scores, and symptoms, in a subpopulation who demonstrated reversibility of FEV<sub>1</sub> upon study entry.

At the time of the start of this study approximately 2260 subjects have been exposed to tralokinumab at various doses and for different periods of time. The ongoing phase 3 trials have contributed more than 1250 of these subjects. 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 defence 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 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 (e.g., 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 IB.

## **1.4 Study Design**

This is an open-label study designed to evaluate the safety of a fixed 300 mg dose of tralokinumab administered SC in subjects with uncontrolled asthma receiving ICS ( $\geq 500$   $\mu\text{g}$  fluticasone propionate dry powder formulation equivalents total daily dose) and a LABA, and having a history of asthma exacerbations.

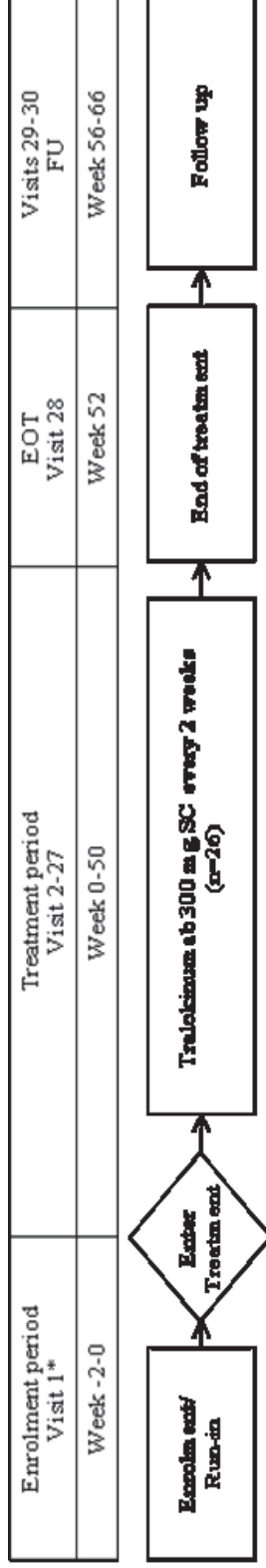
Subjects will receive tralokinumab 300 mg, every 2 weeks via subcutaneous injection at the study site, over a 52-week treatment period.

Approximately 26 subjects will enter treatment at approximately 4 sites in Japan.

After initial enrolment and confirmation of entry criteria, subjects will enter a run-in period of maximum 2 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Subjects who meet eligibility criteria will enter a 52-week treatment period. The first dose of tralokinumab will be administered at Week 0. Subsequent doses will be administered every 2 weeks up until Week 50 (for a total of 26 doses) with an end of treatment (EOT) visit occurring at Week 52. Subjects will be maintained on their currently prescribed ICS-LABA and any additional maintenance asthma controller medications, without change, from enrolment throughout the run-in and treatment period. All subjects will have site visits every 2 weeks.

Follow-up visits will be conducted at Weeks 56 and 66. The extended follow-up period is to ensure adequate determination of immunogenicity.

**Figure 1** Study Flow Chart



\*the run-in period can be maximum 2 weeks in duration

## 2. STUDY OBJECTIVES

### 2.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the safety and tolerability of tralokinumab	<ul style="list-style-type: none"> <li>• Adverse Events (AEs) and Serious Adverse Events (SAEs)</li> <li>• Laboratory variable</li> <li>• Physical examinations</li> <li>• Vital signs</li> <li>• ECG</li> </ul>

### 2.2 Exploratory objectives

Exploratory Objective:	Outcome Measure:
To collect data for the assessment of efficacy of tralokinumab	<ul style="list-style-type: none"> <li>• Asthma Control Questionnaire-6 score (ACQ-6)</li> <li>• Forced expiratory volume in one second (FEV<sub>1</sub>)</li> </ul> <p><b>Key Outcome Variable:</b> Percent change from baseline in pre-dose/pre-BD-FEV<sub>1</sub></p> <ul style="list-style-type: none"> <li>• Asthma exacerbation</li> </ul> <p><b>Key Outcome Measure:</b> Annual asthma exacerbation rate</p>
To explore baseline level and change from baseline of biomarkers	<ul style="list-style-type: none"> <li>• Periostin</li> <li>• Dipeptidyl peptidase-4</li> <li>• Other biomarkers that may be associated with up-regulation of interleukin-13</li> </ul>
To evaluate the pharmacokinetics and immunogenicity of tralokinumab	<ul style="list-style-type: none"> <li>• Serum tralokinumab concentration</li> <li>• Incidence of positive assessments for anti-drug antibodies (ADA) and characterization of their neutralizing potential</li> </ul>

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

### **3. SUBJECT SELECTION, ENROLMENT, TREATMENT, 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 should 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. For subjects aged <20 years a written informed consent should be obtained from the subject and his or her legally acceptable representative.
2. Japanese female and male aged from 12 to 75 years, inclusively at time of enrolment (Visit 1).
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 vasectomized sexual partner, Implanon\*, female sterilization by tubal occlusion, any effective intrauterine device/system (IUD/IUS), Depo-Provera<sup>TM\*</sup> injections, oral contraceptive, and Evra Patch<sup>TM\*</sup> or Nuvaring<sup>TM\*</sup>. WOCBP must agree to use highly effective method of birth control, as define above, from enrolment, throughout the study duration and within 16 weeks after last dose of Investigational Product (IP), and have negative serum pregnancy test result at Visit 1.

\* Not approved in Japan

Women not of childbearing potential are define 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 or more prior to the planned date of enrolment 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 ≥40 and <150 kg at enrolment (Visit 1).

5. Documented physician-diagnosed asthma for at least 12 months prior to enrolment 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).
6. Documented treatment with ICS at a total daily dose corresponding to  $\geq 500$   $\mu\text{g}$  fluticasone propionate dry powder formulation equivalents ( $> 200$   $\mu\text{g}$  for patients with asthma aged 15 years or younger) 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. For ICS-LABA combination preparation, the highest strength approved maintenance dose will meet this ICS criterion.
  - In order to aid the assessment, ICS equivalents for high-dose and medium-dose fluticasone propionate dry powder, as published by the Global Initiative for Asthma (GINA 2016) guidelines, are presented in [Appendix D](#). The Investigator will assess the subject's total daily ICS dose and determine that it corresponds to  $\geq 500$   $\mu\text{g}$  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.

The below defines the minimally acceptable documentation for subject inclusion:

1. Signed and dated notes from a referring physician, including name and dose of the ICS-LABA inhaler (or names and dosages, if used as separate inhalers).
  2. Evidence of prescriptions for ICS-LABA medications that demonstrate coverage for the duration specified in Inclusion criteria 6 and 7.
  3. Documented communication (e.g., phone conversation) clarifying that the subject received treatment with ICS-LABA for asthma. The name, dosage, and duration of use for each medication must be recorded. This option should be used only if reasonable attempts to procure subject records have been unsuccessful.
7. Additional maintenance asthma controller medications are allowed according to standard practice of care. These medications must be stable for one month prior to enrolment (Visit 1). Furthermore, after enrolment, the subject's background maintenance medication for asthma shall remain unchanged throughout the study.
  8. At Visit 1 or 2 the subject must have a pre-bronchodilator (pre-BD)  $\text{FEV}_1$  value of  $\geq 40\%$  of predicted normal value (PNV). Prior to the lung function measurement, the subject should withhold the BD for the effect duration specific to the BD.
  9. At least 1 documented asthma exacerbation in the 12 months prior to the date of the informed consent is obtained that required use of a systemic corticosteroid. In case of



subjects who are re-screened within 30 days of their screen failure date; the 12 months can be calculated from the date that the first informed consent was obtained.

The below defines what is acceptable to document exacerbations:

- Discharge summaries from hospital, emergency department, or an urgent care facility indicating that a subject was hospitalized/treated with systemic steroids for an asthma exacerbation.
- Signed and dated notes from referring physician, including information regarding diagnosis and treatment of an exacerbation with systemic steroids.
- Subjects can provide evidence of prescriptions for system steroids used during an exacerbation.
- A documented conversation between the referral physician or nurse certifying that a subject was treated for an exacerbation with steroids at their clinic or under their supervision. The dates (month/year) of the exacerbations and verbal confirmation that appropriate prescriptions were provided is necessary. This option should be used only if reasonable attempts to procure subject records have been unsuccessful.

A combination of the above is acceptable to document the required exacerbation. However, it is necessary for the Investigator to document how they obtained confirmation of the subject's asthma exacerbation(s). It is the Investigator's responsibility to ensure subject eligibility into the clinical study. In cases where the Investigator feels that alternative records to the above constitutes acceptable documentation, the Study Physician will be contacted for their assessment of eligibility prior to enrolment. Every attempt should be made to obtain appropriate source documentation of medical records.

10. ACQ-6 score  $\geq 1.5$  at Visit 1 or Visit 2.

**Prior to entering treatment at Visit 2, 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 additional asthma controller medication including an increase in ICS dose during run-in.
13. A pre-BD FEV<sub>1</sub> of  $\geq 40\%$  of the subject's PNV at Visit 2, if not met at Visit 1.
14. Ability to perform acceptable inhaler and spirometry techniques.
15. ACQ-6 score of  $\geq 1.5$  at Visit 2, if not met at Visit 1.



## 3.2 Exclusion criteria

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

1. Clinically important pulmonary disease other than asthma (e.g., 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 (e.g., 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 not stable in the opinion of the Investigator and could:
  - 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 enrolment (Visit 1).
6. History of clinically significant infection, including acute upper or lower respiratory infections, requiring antibiotics or antiviral medication within 30 days prior enrolment (Visit 1) or during the run-in period.
7. Tuberculosis requiring treatment within 12 months prior to enrolment (Visit 1).
8. Any clinically significant abnormal findings in physical examination, vital signs, ECG, 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 prior to enrolment (Visit 1), or a condition associated with poor compliance as judged by the Investigator.

10. Confirmed positive test for hepatitis B/hepatitis C serology at screening: a) Hepatitis B surface antigen positive OR b) Hepatitis B core antibody positive with negative hepatitis B surface antibody OR c) Hepatitis C antibody positive. 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, 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  $\geq 3$  months prior to enrolment) or a history of tobacco smoking for  $\geq 10$  pack-years (one pack year = 20 cigarettes smoked per day for 1 year).
13. History of cancer:
  - Subjects who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to enrolment (Visit 1).
  - Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to enrolment (Visit 1).
14. Use of immunosuppressive medication (including but not limited to: methotrexate, troleandomycin, cyclosporine, azathioprine, systemic corticosteroids including regular treatment with OCS or intramuscular long-acting depot corticosteroids, or any experimental anti-inflammatory therapy) within 3 months prior to enrolment (Visit 1).
15. Clinically significant asthma exacerbation, in the opinion of the Investigator, including those requiring use of OCS 30 days prior to enrolment (Visit 1) or during the run-in period.
16. Receipt of immunoglobulin or blood products within 30 days prior to enrolment (Visit 1).
17. Receipt of any marketed or investigational biologic agent within 4 months or 5 half-lives prior to enrolment (Visit 1), whichever is longer.
18. Receipt of live attenuated vaccines 30 days prior to enrolment (Visit 1) and during the study including the follow-up period:
  - Receipt of inactive/killed vaccinations (e.g., inactive influenza) are allowed provided they are not administered within 5 days before/after any dosing visit

19. Receipt of any investigational non-biologic agent within 30 days or 5 half-lives prior to enrolment (Visit 1), whichever is longer.
20. Previous receipt of tralokinumab (CAT-354).
21. Initiation of new allergen immunotherapy or change in existing immunotherapy is not allowed within 30 days prior to enrolment (Visit 1). 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.
22. Current use of oral or ophthalmic non-selective  $\beta$ -adrenergic antagonist (e.g., propranolol).
23. Current use of five-lipoxygenase inhibitors (e.g., Zileuton) or roflumist.
24. Subjects that have undergone bronchial thermoplasty.
25. Major surgery within 8 weeks prior to the enrolment visit, or planned in-subject surgery or hospitalization during the study period.
26. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level  $\geq 2.5$  times the upper limit of normal (ULN) at enrolment.
27. Pregnant, currently breast-feeding, or lactating women.
28. Previous treatment in the present study.
29. Concurrent enrolment in another clinical study where the subject is receiving an IP.
30. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
31. 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.
32. Individuals who are legally institutionalized.

Procedures for withdrawal of incorrectly enrolled subjects see Section 3.4.

### **3.3 Subject enrolment**

Investigator(s) should keep a record (i.e., the subject screening log) of subjects who entered pre-study screening. 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 legal representative, before any study specific procedures are performed.

2. Assign potential subject a unique enrolment code, beginning with 'E#' via the Interactive Web Response System/Interactive Voice Response System (IWRS/IVRS)
3. Determine subject eligibility. See Section 3.
4. Subjects who enter the treatment period will receive tralokinumab. IP will be dispensed via the IWRS/IVRS. Enrolled subjects who discontinue will not be replaced. If a subject withdraws from participation in the study then his/her enrolment code cannot be re-used.

### **3.4 Procedures for handling incorrectly enrolled subjects**

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled 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 initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is enrolled 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 patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

### **3.5 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.
- Subject must abstain from donating blood, plasma from the time of informed consent or assent and for 16 weeks (5 half-lives) after last dose of IP.

### **3.6 Discontinuation of 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<sup>1</sup>
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  $\geq 8$  x ULN
  - b. Confirmed ALT or AST increase of  $\geq 5$  x ULN for more than 2 weeks
  - c. Confirmed ALT or AST increase of  $\geq 3$  x ULN and total bilirubin of  $\geq 2$  x ULN
  - d. ALT or AST of  $\geq 3$  x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ( $\geq 5\%$  increase of differential count of leukocytes)

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 encouraged to continue to undergo all study related visits/procedures for the full 52-week study period in order to support the final 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 events. Complete withdrawal from the study (i.e., withdrawal of consent) has a direct negative impact on the potential validity of all study data and should be avoided wherever possible.

If the subject permanently discontinues IP prior to their completion of the study and wishes to continue with study assessments, they may choose from 3 different follow-up options, as described in Section 4.2.

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<sup>1</sup>A subject is considered lost to follow up when any of the following attempts of contact are failed: 3 attempts of either phone calls, faxes or emails; having sent 1 registered letter/certified mail.

### **3.6.1 Procedures for discontinuation of a subject from investigational product**

At any time, subjects are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments (See Section 3.7), without prejudice to further treatment. A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events by an Investigator(s). They will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 6).

If a subject is withdrawn from study, see Section 3.7.

## **3.7 Criteria for withdrawal**

### **3.7.1 Screen failures**

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not initiate IP. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not patients treated with IP).

### **3.7.2 Withdrawal of the informed consent or assent**

Subjects are free to withdraw from the study at any time (i.e., from receiving IP and/or 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 withdraw, and the presence of any adverse events (AE) by an Investigator(s). The Investigator will follow up AEs outside of the clinical study.

If a subject withdraws from participation in the study, then his/her enrolment 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 (e.g., 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.

## **3.8 Discontinuation of the study**

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,

- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

#### 4. STUDY PLAN AND TIMING OF PROCEDURES

**Table 1 Study Plan**

Assessment/ activity	Enrol- -ment	Treatment																EOT	FU	FU	IPD	UNSP				
		V2 <sup>2</sup>	V3	V4	V5	V6	V7	V8 V9	V10	V11 V12 V13	V14	V15	V16 V17	V18	V19 V20 V21	V22	V23 V24 V25						V26 V27			
	W-2- 0	W0	W2	W4	W6	W8	W10	W12 W14	W16	W18 W20 W22	W24	W26	W28 W30	W32	W34 W36 W38	W40	W42 W44 W46	W48 W50	W52	W56	W66					
		Visit window (days) <sup>4</sup>																								
	N/A	0	+3 -	+3 -	+3 -	+3 -	+3 -	+3 -	+3 -	+3 -	+3 -	+3 -	+3 -	+3 -	+3 -	+3 -	+3 -	+3 -	+3 -	+3 -	+7	+7	N/ A	N/ A		
Informed consent/ assent	X																									
Inclusion/ Exclusion Criteria	X	X																								
Demographics	X																									
Medical and asthma history	X																									
Complete Physical examination	X	X																	X						X	
Brief Physical examination			X	X	X	X	X	X (V9 only)	X	X (V13 only)	X	X	X (V17 only)	X	X (V21 only)	X	X (V25 only)	X (V27 only)		X	X					X
Height	X																		X <sup>5</sup>						X <sup>5</sup>	
Weight	X																		X						X	









## 4.1 Enrolment/Screening period

### 4.1.1 Enrolment (Visit 1)

Each potential subject who is at, or over the age of majority 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, 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 when they have had their BD medications withheld in accordance with the spirometry instructions (see section [5.1.2](#)). The registration of the subject's enrolment via IWRS/IVRS should occur on the day when the 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, exacerbation history, and the current level of control based on an initial ACQ-6 score.

Spirometry will also be performed at Visit 1. Subjects must have a pre-BD FEV<sub>1</sub> value of  $\geq 40\%$  of their PNV in order to proceed in the study (as per section [3.1](#), criterion 8) at Visit 1 or Visit 2. If not, the subject will be screen failed.

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, an ECG, recording the subject's medical/surgical history and concomitant medications, collection of blood samples for haematology/clinical chemistry, serology, collection of a urine sample for urinalysis, and a pregnancy test for WOCBP.

A record of physician-diagnosed asthma, ICS-LABA use, use of other asthma controllers (see section [3.1](#), criteria 5, 6 and 7) and asthmas exacerbations over the prior year (section [3.1](#), criterion 9) is required for source documentation. A subject's verbal history suggestive of asthma symptoms and/or prior asthma exacerbations, but without supporting documentation, is **not** sufficient to satisfy these inclusion criteria.

### 4.1.2 Screening / Run-in (Visit 1-2)

The run-in period (i.e., from Visit 1 - 2) is maximum 2 weeks in duration. The subject should remain on their current asthma treatment with no changes throughout the entire run-in period. Assessments applicable for the run-in period are listed in [Table 1](#).

The subject's eligibility should be evaluated at each visit during the screening/run-in period with the relevant documentation entered in the source and eCRF.

#### **4.1.3 Treatment period (Visit 2)**

Lung function with measurement of pre-BD and post-BD FEV<sub>1</sub> will be performed at Visit 2. Subjects should have a pre-BD FEV<sub>1</sub> of  $\geq 40\%$  of the subject's PNV, if not met at Visit 1.

The subject will complete the ACQ-6 at Visit 2.

#### **4.1.4 Re-screening**

Subjects who experience an asthma exacerbation within 30 days prior to ICF date or during the screening/run-in phase should be screen failed. The subject 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 of informed consent is obtained or during the screening/run-in period may also be re-screened.

Re-screening for the above mentioned reasons is allowed only once for the subject. Subjects should be re-screened no later than 3 months failing initial enrolment.

If the reason for screen failure was transient (including but not limited to equipment failure and unforeseen personal events that mandate missing screening visits), subject 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).

**Re-screening for subjects who have screen-failed due to an ACQ-6 score of  $< 1.5$  is not allowed.**

Any re-screened subject will be enrolled and reassigned their originally assigned enrolment number after signing a new Informed Consent Form (ICF), or assent form, and after all run-in assessments have been performed as listed in [Table 1](#) (with the exception of testing for HIV1, HIV2, hepatitis B and C, and FSH). Re-enrolment is only allowed once for any subject regardless of whether this is due to an exacerbation or infection. The subject may not be re-screened if any other eligibility criteria are failed.

## **4.2 Treatment period**

Inclusion criteria at time for entering treatment period will be confirmed at Visit 2. Before entering treatment period the subject's compliance with their usual asthma controller ICS-LABA and other asthma controller medication must be confirmed (see section 3.1, inclusion criteria 6 and 7).

Subjects confirmed as eligible will enter treatment at Visit 2. Subjects will be administered tralokinumab 300 mg via subcutaneous injection at the study site Q2W for a total of 26 doses.

The first dose of IP will be administered following enrolment through IWRS/IVRS at Visit 2.

The subject will receive 52 weeks of treatment, with the last dose of tralokinumab administered at Visit 27 (Week 50).

Subject will have scheduled visits at 2-week intervals to complete protocol-specific assessments and IP administration, as listed in [Table 1](#). Restrictions as set out in section [7.7.2](#) will continue to apply throughout the treatment period. In case of an asthma worsening/exacerbation (see section [5.1.1](#)), subjects should be evaluated at the study site, when feasible, at an unscheduled visit, or ordinary visit if the worsening happens to fall within a scheduled visit window.

Subjects will have brief physical exams performed at time listed in [Table 1](#). A complete physical exam will be performed at Visit 28 (EOT).

At Week 52 subjects will come to the site for Visit 28 (EOT). The final follow up visits (i.e., 29, and 30) are to occur 4 weeks (+7 days) and 14 weeks (+7 days) from the date of the EOT visit, respectively.

Subjects who prematurely discontinue IP (see section [3.6](#)) should return to the study site and complete procedures described for the IP Discontinuation Visit (IPD visit), see [Table 1](#).

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

1. Ideally, the subject should return for all regular clinic visits and perform all scheduled assessments until he/she completes a total of 52 weeks in the study, or
2. The subject will be followed up on a monthly basis via telephone calls until the subject completes 52 weeks in the study. No other procedures will be performed. Or,
3. The subject will be contacted at 52 weeks post entering the treatment period. No other study assessments will be performed prior to this contact.

For Option 1, all procedures will be done at each visit as indicated in [Table 1](#). For Options 2 and 3, AEs/SAEs, changes in concomitant medications and asthma exacerbation information are the minimum elements that must be collected at each contact.

The subject's and legally acceptable representative'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.

If the subject chooses Option 1, they will complete the IP Discontinuation visit immediately and then the EOT visit at week 52. Should the subject choose Option 2 or 3 above, they will complete the IP Discontinuation visit immediately and then only a follow up telephone call at week 52. For all Options, no follow up visits are required.

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

(i.e., subject initially choosing Option 1, can continue with options 2 or 3, subjects initially choosing Option 2 can continue with Option 3).

Subjects who do not wish to have any follow up contact at all, will be withdrawn from the study.

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

### **4.3 Follow-up period**

Subjects will have follow-up visits (29 and 30) at Weeks 56 and 66, respectively.

## **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 are recorded on the electronic Case Report Forms (eCRF) as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures 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.

### **5.1 Assessments**

#### **5.1.1 Assessment of asthma exacerbations**

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

- Use of systemic corticosteroids for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids
- An ER or urgent care visit (defined as evaluation and treatment for <24 hours in an ED or urgent care center) due to asthma that required systemic corticosteroids (as per above)
- An inpatient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for  $\geq 24$  hours) due to asthma

For the purpose of the protocol, worsening of asthma is defined as new or increased symptoms and/or signs (i.e., physical examination or lung function) that can be concerning to the subject (subject-driven).

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

In order to calculate the number of exacerbations experienced by a subject during the 52-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 visit requiring systemic corticosteroids, or hospital admission due to asthma, whichever occurs earlier, and 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.

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 site for evaluation of a subject-initiated asthma worsening, particularly when it results in additional treatment being prescribed. Study site evaluations for asthma worsening may occur as an unscheduled visit or as part of an ordinary site 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 sites (e.g., by the primary care HCP or at an ED/hospital) and details entered into the exacerbation eCRF module in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the appropriate module of the eCRF.

Maximum follow-up time for a subject is approximately 52 weeks; defined as the time from entering treatment (Visit 2) to the date of Visit 28. For a subject lost to follow-up, this will be defined as the time from entering treatment period to the time point after which an exacerbation could not be assessed (i.e., the last contact date).

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



## 5.1.2 Spirometry

### General requirements

Pulmonary function will be measured by spirometry at the study site using the site's own equipment. Spirometry will be performed by the Investigator or authorized delegate according to the Japanese Respiratory Society (JRS) guidelines ([The Japanese Respiratory Society 2004](#)).

### Time of day for schedule site visit spirometry

Spirometry testing can be initiated anytime throughout the day according to the schedule provided in [Table 1](#). All post-enrolment spirometry assessments should be performed within  $\pm 1.5$  hours of the time that the enrolment spirometry was performed.

**Subjects should be instructed not to use their maintenance twice daily LABA (or ICS-LABA) within 12 hours before the scheduled site visit spirometry** as this will affect the pre-BD FEV<sub>1</sub> value, they may be taken subsequently at the site. For theophylline and once daily BDs a 48 hour washout period is required. **For the same reason, subjects should not use their SABA within 6 hours before scheduled spirometry/ECG assessments.**

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

Subjects that have a spirometry assessment at an unscheduled visit due to a worsening of asthma do not need to follow the washout instructions.

### 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 FEV<sub>1</sub>, 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 consists of three phases, the first is the maximal inspiration, the second is a "blast" of exhalation (to obtain the FEV<sub>1</sub> value) and the last is a continuation to complete exhalation. The subject should inhale rapidly and completely from functional residual capacity. It is important that the preceding inspiration is fast and that any pause at full inspiration be minimal (i.e. only for 1-2 seconds). The subject should be prompted to "blast", not just "blow", and they should be encouraged to fully exhale until the 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.

To allow recording of the FVC value, it is important that the whole manoeuvre lasts for at least 6 seconds. Ensure that none of the following has occurred: coughing during 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 JRS acceptability criteria with the highest value and second highest value for FEV<sub>1</sub> and FVC meeting the reproducibility criteria. The largest FVC and the largest FEV<sub>1</sub> 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 criteria is not fulfilled after the maximum number of manoeuvres has been performed, the highest of the FEV<sub>1</sub> 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 FEV<sub>1</sub> 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.

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

When spirometry is performed the subject's usual asthma controller medication, BD and IP dose, should be withheld until after the final post-BD spirometry are complete.

#### **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 (i.e., if the printout is not on archive-quality paper).

#### **Spirometry references**

FEV<sub>1</sub>, expressed as percent of the PNV, will be calculated as follows:

$$\text{FEV}_1\% \text{ of PNV} = (\text{FEV}_1 \text{ measured} / \text{FEV}_1 \text{ PNV}) \times 100$$

##### **5.1.2.1 Pre-BD and post-BD FEV<sub>1</sub> assessment**

The initial (pre-BD) FEV<sub>1</sub> measurement (Sections 5.1.2) must be completed before commencing the post-BD assessment.

As before, ensure 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 F. If the subject did

not withhold their medications as specified, the post-BD assessment should be rescheduled within the next 7 days; other visit assessments may be completed as planned.

Albuterol 90 µg metered dose or Salbutamol 100 µg metered dose will be used in the post-BD assessment. Up to 4 doses may be administered at Visit 2. The dose should be adjusted if there is any concern about the effect on the subject's heart rate, tremor or any other safety parameter during the assessment; 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.

### **Step 1: FEV<sub>1</sub> measurement after 4 SABA inhalations**

For administration of albuterol/salbutamol, the subject will:

- (i) Perform a gentle, complete expiration
- (ii) Inhale Dose 1 (4 inhalations) of the SABA to TLC and hold their breath for 5-10 seconds before subject exhales.

After resting for 15-20 minutes, proceed to measure FEV<sub>1</sub> following the technique described in Section 5.1.2.

### **5.1.3 Periostin/DPP4**

An investigational use only (IUO)/performance evaluation only (PEO) assay is being specifically developed and validated as a companion diagnostic for tralokinumab to address the potential identification of a target population with an enhanced response rate based on the presence of high serum periostin and/or DPP4 as an indicator of IL-13 driven asthma. The performance characteristics of the assay have not been established. No clinical decision or patient notification should be made based on the results obtained with this product.

A baseline periostin and DPP4 concentration level using the investigational assay may be determined for each subject enrolled in the trial. Analysis will be performed by the central laboratory. Blood sample will be obtained at Visit 2, 8, 15, 28 and IPD visit. These samples may be used in existing and/or future clinical studies in vitro diagnostic assays.

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

## **5.2 Safety assessments**

### **5.2.1 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. Haematology, Clinical chemistry, and Urinalysis samples should be collected at unscheduled visits for assessing 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 chemistry, haematology, and urinalysis tests are presented in [Table 2](#), [Table 3](#), [Table 4](#), and [Table 5](#), respectively.

The following laboratory variables will be measured:

**Table 2 Laboratory Safety Values**

<b>Haematology/Haemostasis (whole blood)</b>	<b>Clinical Chemistry (serum)</b>
B-Haemoglobin (Hb)	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 (BUN)
B-Mean corpuscular volume (MCV)	S- Calcium, total
B-Red blood Cell (RBC) count	S-Carbon dioxide, (CO <sub>2</sub> )
B-HbA1c	S-Chloride
	S-Creatinine
	S-Creatinine kinase
	S-C-Reactive Protein (CRP)
<b>Urinalysis</b>	S-Gamma-glutamyl transpeptidase (GGT)
U-Nitrite (dipstick)	S-Glucose
U-Bilirubin (dipstick)	S-Phosphorus
U-Glucose (dipstick)	S-Potassium
U-Blood (dipstick)	S-Sodium
U-Protein (dipstick)	S-Total cholesterol
U-Ketones (dipstick)	S-Uric acid
Urine microscopy and urine casts (as required*)	
Urine culture (as required*)	

**NB.** In case a subject shows an AST **or** ALT  $\geq 3xULN$  **or** total bilirubin  $\geq 2xULN$  please refer to [Appendix C](#) for further instructions.

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

**Table 3 Clinical Chemistry (serum) Tests schedule**

<b>Visit</b>	<b>V1</b>	<b>V4</b>	<b>V6</b>	<b>V15</b>	<b>V22</b>	<b>V28/ EOT</b>	<b>IPD Visit</b>	<b>UNS Visit</b>
<b>Week</b>	<b>-2-0</b>	<b>4</b>	<b>8</b>	<b>26</b>	<b>40</b>	<b>52</b>	<b>N/A</b>	<b>N/A</b>
ALP	X	X	X	X	X	X	X	X
ALT	X	X	X	X	X	X	X	X
AST	X	X	X	X	X	X	X	X
BUN	X	X	X	X	X	X	X	X
Calcium, total	X					X	X	X
Chloride	X					X	X	X
CO <sub>2</sub>	X					X	X	X
Creatinine	X	X	X	X	X	X	X	X
Creatinine kinase	X							
CRP	X							
GGT	X	X	X	X	X	X	X	X
Glucose	X					X	X	X
Phosphorus	X					X	X	X
Potassium	X					X	X	X
Sodium	X					X	X	X
Total bilirubin	X	X	X	X	X	X	X	X
Total cholesterol	X					X	X	X
Uric acid	X					X	X	X

**Table 4 Haematology/Haemostasis (whole blood) schedule**

VISIT	V1	V3	V4	V6	V8	V10	V12	V14	V16	V18	V20	V22	V24	V26	V28	V29	V30	IPD	UNS
Week	-2-	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	66	N/A	N/A
															(EOT)	(FU)	(FU)	Visit	Visit
B-Haemoglobin	X	X	X	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	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	X	X	X
B-Platelet count	X	X	X	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	X	X	X
B-Mean corpuscular volume	X	X	X	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	X	X	X
B-HbA1c																			X

**Table 5 Urinalysis schedule**

<b>VISIT</b>	<b>V1</b>	<b>V4</b>	<b>V6</b>	<b>V15</b>	<b>V22</b>	<b>V28 (EOT)</b>	<b>IPD Visit</b>	<b>UNS Visit</b>
<b>Week</b>	<b>-2-0</b>	<b>4</b>	<b>8</b>	<b>26</b>	<b>40</b>	<b>52</b>	<b>N/A</b>	<b>N/A</b>
U-Nitrite (dipstick)	X	X	X	X	X	X	X	X
U-Bilirubin (dipstick)	X	X	X	X	X	X	X	X
U-Glucose (dipstick)	X	X	X	X	X	X	X	X
U-Blood (dipstick)	X	X	X	X	X	X	X	X
U-Protein (dipstick)	X	X	X	X	X	X	X	X
U-Ketones (dipstick)	X	X	X	X	X	X	X	X
Urine microscopy and urine casts (as required)*								
Urine culture (as required)*								

\* Urine samples will be analysed locally 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 6](#).

**Table 6** Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume <sup>2</sup> (mL)
Safety	Clinical chemistry	2.5	6	15
	Haematology (including HbA1c)	2	17	34
FSH, $\beta$ -HCG <sup>1</sup>		1	1	1
Serology		7.5	1	7.5
IgE		2.5	2	5
Phadiatop <sup>®</sup>		2.5	1	2.5
Periostin		6	4	24
DPP4 and other biomarkers		10	4	40
ADA/nAb		3.5	5	17.5
PK		3.5	6	21
<b>Total</b>				167.5

<sup>1</sup> Female subjects only

<sup>2</sup> The number of samples may be changed due to additional sampling at unscheduled visits, and the blood volume required may be altered to fit the assay requirements.

Urine will be tested locally and sent for analysis at the central lab only when a positive dipstick result for any parameter is observed. Blood samples for determination of haematology/haemostasis and clinical chemistry will be performed at a central laboratory. For information on methods of collection, assessment, labelling, storage and shipment of samples, please refer to the separate Laboratory Manual.

A copy of the laboratory result report should be signed and dated by the Investigator and retained at the study site.

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](#).



### **5.2.2 Pregnancy Test**

The following tests are applicable to female subjects only, and will be conducted in accordance with the schedule provided in [Table 1](#).

- Serum  $\beta$ -human chorionic gonadotropin ( $\beta$ -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.
- 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 results must be confirmed with serum  $\beta$ -HCG.

### **5.2.3 Physical examination**

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

Baseline data will be collected at Visit 1. 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](#).

#### **5.2.3.1 Complete physical examination**

The complete physical examination will be performed and 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.

#### **5.2.3.2 Brief physical examinations**

The brief physical examination will include an assessment of the general appearance, abdomen, cardiovascular and respiratory system.

### **5.2.4 ECG**

All ECG assessments must be performed using an electrocardiogram (ECG) device. ECGs will be performed in accordance with schedule provided in [Table 1](#). ECG assessments will be performed prior to blood drawing, spirometry, IP administration and BD administration.

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

#### **5.2.4.1 Resting 12-lead ECG**

A 12-lead ECG 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 (e.g., spirometry and administration of asthma-related medications and IP).

A standard ECG with Data will be frozen and then locked to prevent further data entry/editing a recommended paperspeedof25mm/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 ECG findings. In case of discrepancy between the Investigator's interpretation and that provided by the ECG 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 ECG 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 ECG assessments throughout the subject's participation in the study.

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

#### **5.2.5 Vital signs**

Pre-dose vital signs (i.e., pulse, blood pressure, respiration rate and body temperature) will be obtained in accordance with schedule provided in [Table 1](#).

Vital signs will be taken prior to blood drawing, IP administration, and, if possible, usual asthma controller medication. At Visits 2 through 6, 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.

##### **5.2.5.1 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 (i.e., how many times the chest rises) for one minute.

##### **5.2.5.2 Body temperature**

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

## **5.2.6 Other safety assessments**

### **5.2.6.1 Serology**

Hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, 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.

### **5.2.6.2 Infections**

The severe infections, defined as/resulting in:

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

must be entered in the infection module in the eCRF.

## **5.3 Other assessments**

### **5.3.1 Weight and height**

Weight and height will be measured in accordance with the schedule provided in [Table 1](#).

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.

### **5.3.2 Patient reported outcomes**

Patient reported outcomes data will be captured on paper. Additional details concerning the assessment can be found in the subsequent sections [5.3.2.1](#).

#### **5.3.2.1 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  $\beta_2$ -agonist use) omitting the FEV<sub>1</sub> 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  $\leq 0.75$  indicate well-controlled asthma, scores between 0.75 and  $< 1.5$  indicate partly controlled asthma, and a score  $\geq 1.5$  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 on paper.

ACQ-6 score of  $\geq 1.5$  is required either at Visit 1 or 2 to determine eligibility to enter the treatment period (see section 3.1, inclusion criteria 10). Once enrolled, subjects will be asked to complete the ACQ-6 once approximately every 14 weeks throughout the treatment period (see Table 1, Study Plan).

The Investigator/authorized delegate will provide the ACQ-6 questionnaire to the subject at each visit shown in Table 1 and review for completeness.

## **5.4 Pharmacokinetics and Immunogenicity**

### **5.4.1 Collection of samples**

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

Instructions for sample collection, labelling, 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 6.

### **5.4.2 Determination of drug concentration**

Samples for determination of tralokinumab concentration in serum will be analysed 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.

### **5.4.3 Storage and destruction of pharmacokinetic samples**

Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, 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 [REDACTED]; see details in the Laboratory Manual).

#### **5.4.4 Immunogenicity**

Instructions for immunogenicity (ADA/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-drug antibodies**

The pre-dose serum samples to measure presence of ADA will be collected according to the schedule of study procedures (see [Table 1](#)).

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 analysed for the presence of nAb.

#### **Neutralizing antibodies (nAb)**

Neutralizing antibodies will be assessed at Visits 2, 15, 28 (EOT), 29 and 30 (Weeks 0, 26, 52, 56, and 66, respectively) according to the tiered testing scheme outlined above.

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.

#### **5.4.5 Total IgE**

Testing for IgE will be performed at Visits 2, 28 (EOT) (Weeks 0 and 52, respectively) and IPD according to the schedule of study procedures (see [Table 1](#)).

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

#### **5.4.6 Phadiatop<sup>®</sup>**

Testing for phadiatop<sup>®</sup> will be performed at Visit 2 (Week 0).

The analysis for these will be performed by central laboratory. Instructions for sample collection, processing, storage, and shipment will be provided in a separate Laboratory Manual provided to the sites.

### **5.5 Biomarkers**

Blood (serum) samples will be collected pre-dose according to the schedule in [Table 1](#), 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.

### **5.6 Biological Samples**

The subject's consent or assent to the use of donated biological samples is mandatory.

Biological samples (i.e., blood, plasma, serum) will be collected and may be analysed 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 ensures 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 B](#) '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 is maintained for all samples throughout their lifecycle.

The Principal Investigator, or delegate, at each site will keep 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 keeps full traceability of the samples while in storage and during use until used, or disposed of, or until further shipment and keeps documentation of receipt of arrival.

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

Samples retained for further use are registered in the Fisher Bioservices, or designate, during the 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 donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, 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:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented

- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned 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 adverse event 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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., 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.

For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected.

### **6.2 Definitions of serious adverse event**

A serious adverse event is an AE occurring during any study phase (i.e., 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 hospitalisation or prolongation of existing hospitalisation
- 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 A](#) to the Clinical Study Protocol.

## **6.3 Recording of adverse events**

### **6.3.1 Time period for collection of adverse events**

Adverse Events including Serious Adverse Events will be collected from the time the subject signs the informed consent or assent form, throughout the treatment period and the follow-up periods i.e., Visit 29 (week 56) and Visit 30 (week 66).

### **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 investigational product
- 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 for serious AE
- Date Investigator became aware of serious AE
- 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 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 Investigational Product 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 found in [Appendix A](#) 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 summarised in the clinical study report. 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 uses the clinical, rather than the laboratory term (e.g., 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  $\geq 3$ xULN together with total bilirubin  $\geq 2$ xULN may need to be reported as SAEs. Please refer to [Appendix C](#) 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 after enrolment/treatment, unless it fulfils any of the above criteria. All asthma exacerbations should be recorded in the exacerbation eCRF as per section 5.1.1.

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 the study on the AE form.

## 6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

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

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient 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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., 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 is 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 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

Overdose for this trial is defined as any dose of Tralokinumab over 600 mg SC given in a period of 14 days. An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

An over dose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative(s) works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient 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 (including outcome of the pregnancy) in subjects 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 informs the appropriate AstraZeneca representatives within 1 day (i.e., immediately) but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works 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 is 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 E.

Anaphylaxis will be defined as serious reaction that is rapid onset and may cause death (Sampson et al 2006). Anaphylaxis typically manifest as one 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 (i.e., vital signs and lung function) prior to IP administration. At Visits 2 through 6, 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.

If any anaphylactic reaction occurs, 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 as per Table 1 for this visit). A blood sample will be drawn from the subject as soon as possible after the event, at 60 minutes  $\pm$  30 minutes after the event, and at discharge for analysis of serum tryptase. The serum tryptase will be tested at the local lab or central lab where applicable.

## **7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS**

### **7.1 Identity of investigational product(s)**

All investigational product will be manufactured in accordance with GMP.

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

Subjects will enter treatment at Visit 2 (Week 0), and will receive tralokinumab 300 mg, Q2W (26 doses).

Each subject will receive two injections of 150 mg tralokinumab at each dosing interval to receive a total dose of 300 mg. The identity details for the IP are found in [Table 7](#).

**Table 7 Identity of Investigational Product**

<b>Investigational product</b>	<b>Concentration and Formulation</b>	<b>Dosage form and strength</b>	<b>Manufacturer</b>
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

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 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 long pre-filled syringe barrel with a ½ inch 27 gauge (approximately 13 mm) thin wall staked in needle, rigid needle shield, plunger stopper) and a safety device. The PFS-SA is an unapproved device in Japan.

## **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 1](#). A minimum interval of 7 days is required between 2 dosing visits.

### **IP administration**

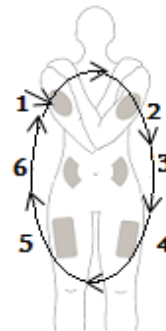
IP will be administered by a qualified, healthcare professional. The two injections should be administered within the same body location, separated by at least 3 cm. The injection site must be recorded in the source documents at each treatment visit and recorded in the eCRF.

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 2](#).

**Figure 2 Injection sites and rotation scheme**



In cases when rotation of the injection site is not favourable 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.

#### **Post IP Administration (Visits 2-6)**

At each visit, the subject will be observed for the appearance of any acute drug reactions, for a minimum of 2 hours with vital signs taken every 30 minutes, until stable.

#### **Post IP Administration (Visits 7-27)**

At each visit, the subject will be observed for the appearance of any acute drug reactions, for a minimum of 1 hour with vital signs taken every 30 minutes, until stable.

#### **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  $\geq 38^{\circ}\text{C}$ ;  $\geq 100.4^{\circ}\text{F}$ ) within 72 hours prior to IP administration

### **7.3 Labelling**

Labelling of the IP will be carried out by AstraZeneca or designees in accordance with current GMP. Labels will be prepared in accordance with GCP Ordinance. Details are specified in the document explaining the reconstitution procedures and other handling procedures for the investigational products.

### **7.4 Storage**

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

A description of the appropriate storage conditions is specified in the document explaining the reconstitution procedures and other handling procedures for the investigational products.

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

Site staff should not use the affected IP, and should immediately contact their AstraZeneca representative for further guidance in the following cases:

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

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**

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for

managing the study drug from receipt by the study site until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage' which describes the specific requirements. The Investigator(s) is responsible for ensuring that the subject has returned all unused study drug.

A qualified healthcare professional at the site, or the AstraZeneca monitor will account for they study drug received at the site, unused study drug and for appropriate destruction. Certificates delivery and return should be signed.

In case of malfunctioning APFS, the centre should contact the 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 subject's informed consent or assent, 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 (as shown in [Table 1](#)), and recorded in the eCRF.

**Note:** to satisfy inclusion criterion 6, the history of continuous treatment with ICS corresponding to  $\geq 500$   $\mu\text{g}$  fluticasone propionate dry powder formulation equivalents plus a LABA for at least 3 month prior to Visit 1 should be documented in source and recorded in the eCRF (see section [3.1](#) and [4.1.1](#)).

### Maintenance of asthma controller medication

All subjects are required to be treated with a dose of ICS corresponding to  $\geq 500$   $\mu\text{g}$  fluticasone propionate dry powder formulation equivalents (as outline in [Appendix D](#)) 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 evaluate the safety of tralokinumab as an add-on treatment and therefore the maintenance asthma controller therapy should be maintained at a stable dose from Visit 2 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 the source along with rational for change and recorded in the 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.

Subjects on maintenance treatment with theophylline should have a documented blood concentration levels with 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 $\beta_2$ -agonists (SABA)**

Regularly scheduled SABA use in the absence of any asthma symptoms is discouraged from enrolment 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. 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). Any such use should be documented in medical notes and recorded in the eCRF.

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. Any such use should be documented in medical notes and recorded in the eCRF.

#### **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 enrolment and throughout the study duration.

#### **Use of theophylline and once daily bronchodilators**

Use of theophylline and once daily BDs is allowed at the discretion of the Investigator. However, use of these drugs should be stabilized as least 1 month prior to the subject entering the study. Also, a 48 hour minimum wash-out period is required before spirometry if a subject is using theophylline or a once-daily BD. Should the subject be taking theophylline or the 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.

### **Asthma medication restrictions on the days of scheduled site visit spirometry**

Pre- and/or post-dose spirometry assessments will be performed at the study site at scheduled visits (see [Table 1](#)). Restriction to a subject's maintenance medication is required prior to the spirometry as described below (also see section [5.1.2](#)):

#### **Visit 1**

Subjects will be asked to withhold their twice daily BD therapy (including ICS-LABA) for 12-24 hours prior to the assessment of FEV<sub>1</sub> for eligibility (see Section [3.1](#), Inclusion criteria 8). For once daily BDs the required washout is  $\geq 48$  hours.

#### **Treatment period (Visit 2 – 27)**

Subjects will be asked to withhold their usual BD and SABA as outlined in the section above for Visit 1.

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 [5.1.2](#).

If the subject has taken their usual ICS-LABA and/or any other BD without appropriate washout period (see Visit 1 above) before the 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. If neither of these options is feasible for the subject, spirometry may be performed with a notation indicating that the pre-BD spirometry was conducted within 6 hours of SABA use.

#### **Asthma medication restrictions on unscheduled visits**

Asthma medication restrictions on unscheduled visit 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 ECG assessment**

Subjects should be instructed not to take their usual asthma controller medication prior to scheduled ECG assessment. Use of SABA should be avoided within 6 hours prior the ECG assessment.

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

### 7.7.2.2 Other medication restrictions

- Use of oral or systemic immunosuppressive medication is not allowed. Topical administration of immunosuppressive medication may be allowed at the discretion of the Investigator. Systemic corticosteroids are allowed in case of an asthma exacerbation. Please see section 3.2, Exclusion criteria 14 and 17, for examples and further details.
- Receipt of live attenuated vaccines within 30 days prior to entering study treatment and during the study, including the follow up period, is not allowed. Inactive/killed vaccines (e.g., 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 within 5 days before/after any dosing visit.
- Subjects should not take any other excluded medications:
  - Oral or ophthalmic non-selective  $\beta$ -adrenergic antagonist (e.g., propranolol)
  - Five-lipoxygenase inhibitors (e.g., Zileuton), or roflumilast

A table with medication-related restrictions is present in [Appendix F](#).

### 7.7.2.3 Bronchial Thermoplasty

Subjects should not undergo bronchial thermoplasty during the entire study (Visit 1 to Visit 30).

### 7.7.3 Other treatments

Other treatments which are considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator. Any such treatments are to be recorded in the appropriate section of the eCRF.

## 8. STATISTICAL ANALYSES BY ASTRAZENECA

### 8.1 Statistical considerations

The main objectives of this study are to show safety and tolerability of tralokinumab with regards to AEs, SAEs, laboratory variables, physical examination, vital signs and ECG.

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

## 8.2 Sample size estimate

No formal sample size calculation was conducted for this study. Approximately 22 Japanese patients who complete the planned 52-weeks treatment period are considered appropriate for collecting additional safety information of tralokinumab (300 mg SC Q2W) among Japanese patients. With an assumed drop-out rate of 15% during the 52-weeks treatment period, approximately 26 Japanese patients are needed to be dosed.

The interim and final analyses of the study are primarily described using descriptive statistics. Where appropriate, an exact 95% confidence interval (CI) may be calculated. No hypothesis testing will be conducted for this study.

## 8.3 Definitions of analysis sets

Safety objectives will be analyzed based on the Safety population. Exploratory 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.

### 8.3.1 Efficacy analysis set

**Full analysis set:** All subjects receiving any IP will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. 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 at least one dose of investigational product will be included in the safety analysis set. All safety summaries and ADA analyses and summaries will be based on this analysis set.

### 8.3.3 PK analysis set

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

### 8.3.4 PRO analysis set

PRO exploratory 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

For laboratory data, baseline will be defined as the latest non-missing assessment prior to start of treatment.

For spirometry variables, the measurement recorded at the baseline visit (Visit 2) will be used as baseline. If the Visit 2 measurement is missing, the last non-missing value before Visit 2 will be used as baseline instead. For post-BD FEV<sub>1</sub>, the measurement after the first BD administration is the baseline.

The baseline for the PRO variable, ACQ-6 will be collected at Visit 2.

Absolute change from baseline is computed as (post-treatment value – baseline value).

Percent change from baseline is computed as ((post-treatment value – baseline value) / baseline value) × 100%. If either the post-treatment 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 summaries no windows will be applied.

For patient reported questionnaire ACQ-6, 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 Exacerbation rate**

Asthma exacerbation is defined in Section 5.1.1. In order to calculate the number of exacerbations experienced by a subject during the 52-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 corticosteroids, or hospital admissions due to asthma, whichever occurs earlier, and 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 52 weeks; defined as the time from start of study treatment to the date of Visit 28. For a subject lost to follow-up, this will be



defined as the time from start of study treatment 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 2 date + 1).

#### **8.4.2.2 Forced expiratory volume in 1 second**

The percent change from baseline in pre-dose/pre BD FEV<sub>1</sub> to each of the post-treatment visits (post Visit 2), up to and including the end of 52-week treatment visit (Visit 28), will be used as an exploratory efficacy variable.

The absolute change from baseline to each of the post-treatment visits (post Visit 2) up to and including the end of 52-week study treatment visit (Visit 28) will also be used as an exploratory efficacy variable.

The same exploratory efficacy variables will be derived for pre-dose/post- BD FEV<sub>1</sub>.

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

Patient-reported outcomes data will be captured on paper and entered into the WBDC system.

##### **8.4.3.1 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, use of short acting  $\beta$ -agonists 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 ACQ-6 score is 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  $\leq -0.5$
  - Non-responder : Change from baseline ACQ-6 score  $> -0.5$
- ACQ-6-responder (improved/No Change / Deterioration)
  - Improvement: Change from baseline ACQ-6 score  $\leq -0.5$
  - No change:  $-0.5 < \text{Change from baseline ACQ-6 score} < 0.5$
  - Deterioration: Change from baseline ACQ-6 score  $\geq 0.5$
- Subjects asthma control as measured by ACQ-6 score:
  - Well controlled : ACQ-6 score  $\leq 0.75$
  - Partly controlled :  $0.75 < \text{ACQ-6 score} < 1.5$
  - Not well controlled : ACQ-6 score  $\geq 1.5$

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

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

Change from baseline (Visit 2) to each post-baseline time point where scheduled assessments were made will be calculated for relevant measurements.

##### **8.4.4.1 Adverse events**

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

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

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

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.

#### **8.4.4.2 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 haematological and other laboratory abnormalities, and certain events that led to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

#### **8.4.4.3 Laboratory variables**

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times detailed in the CSP, and will be assessed in a central laboratory. The parameters outlined in [Table 2](#), [Table 3](#), [Table 4](#) and [Table 5](#) in Section 5.2.1, 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 is defined as the last available value measured prior to the first dose of study treatment. The change from baseline is 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 start of treatment, 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.

Multiple = Value / ULN

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

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

- AST  $\geq 3$ x ULN
- ALT  $\geq 3$ x ULN
- TBL  $\geq 2$ xULN

#### 8.4.4.4 ECG

Twelve-lead ECG 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.

#### 8.4.4.5 Physical examination

Complete and brief physical examinations will be performed at time points specified in [Table 1](#). Only information on whether the assessment was performed or not will be recorded.

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

#### 8.4.4.6 Vital signs

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

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 study 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:

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

#### **8.4.5 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 IP administration at Visit 2, at multiple time points before IP administrations during the treatment period, and at selected time points in the follow-up phase of the study. Anti-drug antibodies assessments will be conducted utilizing a tiered approach (screen, confirm, titer). These validated methods are conducted using a bridging assay format and statistically determined floating screening assay cut point factor and confirmatory assay cut point. The minimal sample dilution is 1:13. Titer values are reported as the reciprocal of the highest dilution that yields a value above the cut point. Samples from pre-defined study time points that confirm positive for ADA will also be tested for neutralizing ADA/nAb activity. Both ADA and nAb will be summarized using descriptive statistics as described in Section 8.5.2.4.

#### **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 analysis of the study endpoints will include all data captured during the entire study 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.

Summary data will be presented in tabular format. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables for parametric data will be summarized by descriptive statistics including N, mean, SD, median, and range. All data will be listed. Data listings will be sorted by subject number.

#### **8.5.1 Safety and tolerability**

All safety variables will be summarized using the safety analysis set.

##### **8.5.1.1 Adverse events**

AEs will be summarized separately for the treatment and study 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, 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 (i.e., accounting for multiple occurrences of the same event in a subject).

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

AEs (by 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.

#### **8.5.1.2 Laboratory data**

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

AstraZeneca defined 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.

#### **8.5.1.3 ECG**

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

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

#### **8.5.1.4 Vital Signs**

Vital signs data will be presented in the same way as described in Section 8.5.1.2 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.

### **8.5.2 Exploratory analysis**

Exploratory analyses will be based on the following analysis sets: all analyses of efficacy variables will be based on the full analysis set, all analyses of pharmacokinetic variables will be based on the PK analysis set, and all analyses of Immunogenicity variables will be based on the safety analysis set.

#### **8.5.2.1 Exacerbation Rate**

The annual exacerbation rate, as described in section 8.4.2.1, will be summarized descriptively at week 52. The individual exacerbation criteria (ER or UC visits due to asthma that required

systemic corticosteroids, hospitalization due to asthma, or use of systemic corticosteroids) will be summarized descriptively.

#### **8.5.2.2 Lung Function**

The percent change from baseline in pre-dose/pre-BD FEV<sub>1</sub> will be summarized descriptively by visit. Summary statistics for pre-dose/pre-BD FEV<sub>1</sub>, including the change from baseline will be summarized descriptively by visit.

Pre-dose/post-BD FEV<sub>1</sub> will be summarized as described above for pre-dose/pre-BD FEV<sub>1</sub>.

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

Change in mean score from baseline for ACQ-6 will be summarized descriptively by visit. The mean ACQ-6 score will also be summarized descriptively by visit.

The number and percentage of subjects achieving mean ACQ-6  $\leq 0.75$ ,  $0.75 < \text{mean ACQ-6} < 1.5$  and mean ACQ-6 of  $\geq 1.5$  at EOT will be summarized. Additionally, the number and percentage of subjects achieving an improvement, no change, or deterioration as per Section 8.4.3.1, ACQ-6 will also be summarized.

#### **8.5.2.4 Analysis of Immunogenicity variables**

ADA status (positive vs negative) at each visit will be summarized descriptively including number of subjects, mean, standard deviation, median, and range of the actual ADA titers by visit, where possible, will be provided. The ADA status across the study for each subject (positive vs negative) will also be classified and summarized. 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. The ADA-positive subjects across the study may also be divided into persistent positive versus transient positive. A subject will be considered as persistent positive if he/she has positive ADAs for at least two consecutive visits. 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.



### **8.5.3 Analysis of pharmacokinetics**

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

### **8.6 Interim Analysis**

An interim analysis may be conducted for this study. Interim results of the study may be included for communication with regulatory authorities, where required/requested.

## **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 staff and also train them on any study specific procedures, the WBDC system RAVE and IVRS/IWRS, PRO.

The Principal Investigator will ensure that appropriate training relevant to the study is given 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 maintain a record of all individuals involved in the study (medical, nursing and other staff).

### **9.2 Monitoring of the study**

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that 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 of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)



- Ensure withdrawal of informed consent 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 staff at the centre needs information and advice about the study conduct.

### **9.2.1 Source data**

Source data are any data generated as a result of the subject's inclusion in the study (including run-in and/or follow up related to the study) and includes all related medical examinations and other records.

### **9.2.2 Study agreements**

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

## **9.3 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 4Q 2016 and to end by 2Q 2018. The study may be terminated at individual centres if the study procedures are not being performed according to 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 Data Management Plan 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 RAVE 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 be 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. All entries to the study database will be available in an audit trail. When all data have been coded, validated, signed and locked, clean file will be declared. Data will be frozen and then locked to prevent further data entry/editing. A copy of the eCRFs will be provided to an archived at the study site when the study has been locked.

The 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 the Medical Dictionary for Regulatory Activities (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 are produced and reconciled with the Patient 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 (e.g., paper PRO, 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 ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

## **10.2 Subject data protection**

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

## **10.3 Ethics and regulatory review**

An IRB should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The head of the study site will ensure the distribution of these documents to the applicable IRB, and the Principal Investigator to the Investigator and study site staff.

The opinion of the IRB should be given in writing. The head of the study site should submit a notification of direction/determination as well as the IRB written approval to AstraZeneca and the Principal Investigator before enrolment of any subject should into the study.

The IRB should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

The head of the study site should seek the opinion of the IRB with respect to the appropriateness of continuing the study at the study site at least once a year when the duration of the study exceeds one year. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

Before enrolment of any subject into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority with notification provided, according to local regulations. AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, IRB, the head of the study site and the Principal Investigator with safety updates/reports according to local requirements.

The head of the study site should submit a written report to the IRB providing the details of all safety relative information reported by AstraZeneca.

## **10.4 Informed consent and assent**

The Principal Investigator(s) at each centre 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 before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is 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 form that is approved by an IRB.

### **10.5 Changes to the protocol and informed consent or assent form**

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the Clinical Study Protocol to be amended, the amended Clinical Study Protocol should be submitted to the Head of the Study Site. If the changes are of an administrative nature, it is submitted to the IRB. If the changes have a significant impact on the safety of the subjects, the scientific value of the study, the conduct and management of the study, and the quality of any investigational product used in the study, it should be approved by the IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If the amended Clinical Study Protocol requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB should be notified by the Principal Investigator. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used.

### **10.6 Audits and inspections**

Authorised representatives of AstraZeneca, a regulatory authority, or an IRB may perform audits or inspections at the centre, 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, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the site.

## 11. LIST OF REFERENCES

### **Accordini et al 2006**

Accordini S, Bugiani M, Arossa W, Gerzeli S, Marinoni A, Olivieri M, et al. Poor control increases the economic cost of asthma. A multicentre population-based study. *Int Arch Allergy Immunol.* 2006;141(2):189-98. Epub 2006 Aug 4.

### **Bateman et al 2010**

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## **Appendix A 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 hospitalization
- 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.



## **Appendix B 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. 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
- 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.

## **Appendix C    Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law**

### **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. Specific guidance on the managing liver abnormalities can be found in Section 6.3.7 of the protocol.

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.

### **Definitions**

#### **Potential Hy's Law (PHL)**

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT)  $\geq 3x$  Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL)  $\geq 2xULN$  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  $\geq 3x$  ULN **together with** TBL  $\geq 2xULN$ , 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.

### **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  $\geq 3xULN$

- $AST \geq 3xULN$
- $TBL \geq 2xULN$

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:

- 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 [Definitions](#) within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

### **Follow-up**

#### **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.

#### **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

### **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

## 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>

## Appendix D Maintenance Therapy Equivalence Table

### Estimated Daily Doses for Inhaled Corticosteroids

**Table 8** Estimated daily doses for inhaled corticosteroids

Asthma Therapy Inhaled Corticosteroid	Total Daily Dose (µg/day)	
	Medium <sup>1</sup>	High
Beclomethasone dipropionate	>500 - <b>1000</b>	>1000 - 2000
Beclomethasone HFA	>240 - <b>480</b>	>480
Beclomethasone dipropionate (Fostair)	>200 - <b>400</b>	>400 - 800
Ciclesonide	>160 - <b>320</b>	>320 - 1280
Triamcinolone acetonide	>1000 - <b>2000</b>	>2000
Flunisolide	>1000 - <b>2000</b>	>2000
Fluticasone fuorate	<b>100</b>	200
Fluticasone propionate	>250 - <b>500</b>	>500 - 1000
Fluticasone propionate HFA	>364 - 440	>440
Budesonide	>400 to <b>800</b>	>800 - 1600
Budesonide, if as delivered dose (eg Symbicort <sup>®</sup> )	>320 to <b>640</b>	>640 - 1280
Mometasone furoate	≥400	≥800

<sup>1</sup> The acceptable medium ICS dose for this study is bolded.

## **Appendix E 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, corticosteroid, etc, and medical equipment to treat anaphylactic reactions must be immediately available at the 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  $\pm$  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-bronchospasma, 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**

##### **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.

##### **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

##### **Specific measures to consider after epinephrine injections, where appropriate**

- a) Consider epinephrine infusion.
- b) Consider H1 and H2 antihistamines.
- c) Consider nebulized  $\beta_2$  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.

## **References**

### **Johansson et al 2004**

Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol*. 2004May;113(5):832-6

## Appendix F Restricted and Prohibited Medications

### Asthma medication restrictions

**Table 9 Asthma medication restrictions**

Medication	Prohibited/Restricted	Details
Maintenance treatment with long-acting bronchodilators (including ICS-LABA)	Restricted	<p>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).</p> <p>Usual ICS-LABA should not be taken prior to scheduled spirometry, and ECG (to be administered once assessments are completed).</p> <p>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.</p>
Short acting beta-agonists (SABA)	Restricted	<p>Regular scheduled use not allowed from enrolment through the study duration.</p> <p>Rescue use of SABA administered via nebulization is discourage, except as urgent treatment during an asthma exacerbation.</p> <p>SABA should not be used within 6 hours prior to scheduled site visit spirometry and ECG with the exception of any unscheduled visits due to asthma worsening.</p>

<b>Medication</b>	<b>Prohibited/Restricted</b>	<b>Details</b>
Additional Maintenance Controllers	Allowed with restriction	<p>Stable dose for 1 month prior to Visit 1; stable dose during the treatment period.</p> <p>Subjects on theophylline should have blood concentration levels within therapeutic range documented before/at Visit 1.</p> <p>Subject should be instructed not to use additional once daily bronchodilators within 48 hours of the scheduled site visit spirometry with the exception of any unscheduled visits due to asthma worsening.</p>
Short acting anticholinergics (i.e., ipratropium)	Restricted	<p>Not allowed from enrolment and throughout the study as a rescue treatment for worsening asthma symptoms outside of managing an asthma exacerbation event.</p> <p>May be used for managing an asthma exacerbation event.</p>
Zileuton	Prohibited	Not allowed 30 days prior to Visit 1; during treatment period

### Other medication restrictions

**Table 10** Other medication restrictions

<b>Medication</b>	<b>Prohibited/Restricted</b>	<b>Details</b>
Live Attenuated Vaccines	Prohibited	Not allowed 30 days prior to entering treatment, during treatment and follow up periods.
Inactive/killed vaccinations (e.g., inactive influenza)	Restricted	Allowed provided they are not administered within 5 day before or after any dosing visit
Any immunomodulators or immunosuppressives	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

<b>Medication</b>	<b>Prohibited/Restricted</b>	<b>Details</b>
Blood products or immunoglobulin therapy	Prohibited	Not allowed 30 days prior to the date of ICF; during treatment period
Any marketed (e.g., omalizumab) or investigational biologic treatment	Prohibited	Not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1; 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
Allergy Immunotherapy	Restricted	Allowed if on stable therapy for at least 30 days prior to date of ICF; no anticipated changes during treatment period; subject should not receive allergen immunotherapy injection within 5 days before/after any dosing visit
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 $\beta$ -adrenergic antagonist (e.g., propranolol)	Prohibited	Patients currently using any oral or ophthalmic non-selective $\beta$ -adrenergic antagonist at the time of enrolment are not eligible for the study.  Not allowed during treatment period.
Medications not currently licensed for use in the treatment of asthma 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

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Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.