A Phase 2b, Randomized, Double-blind Study to Evaluate the Efficacy of Tralokinumab in Adults with Uncontrolled, Severe Asthma

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ACQ-6	Asthma Control Questionnaire (6-item version)
ADA	anti-drug antibodies
AE	adverse event
AHR	airway hyperresponsiveness
AQLQ(S)	Asthma Quality of Life Questionnaire (Standardised Version)
ASMA	Assessing Symptoms of Moderate-to-severe Asthma
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
βHCG	β human chorionic gonadotrophin
BMI	body mass index
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COPD	chronic obstructive pulmonary disease
CRF	case report form
CT	computed tomography
DPI	dry powder inhaler
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ePRO	electronic Patient-reported Outcome
ERS	European Respiratory Society
EU	European Union
FEIA	Fluorescent Enzyme Immunoassay
FEV_1	forced expiratory volume in 1 second
FEV_6	forced expiratory volume in 6 second
FVC	forced vital capacity
HIPAA	Health Insurance Portability and Accountability Act
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HIV	human immunodeficiency virus
HRCT	high-resolution computed tomography

Abbreviation or Specialized Term	Definition
HRQoL	health-related quality of life
HRU	Healthcare Resource Utilization
IC	inspiratory capacity
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid(s)
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgG4	immunoglobulin G4
IgE	immunoglobulin E
IL-13	interleukin-13
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IXRS	interactive voice/web response system
LABA	long-acting β2 agonist
MAb	monoclonal antibody
MDI	metered dose inhaler
mRNA	messenger ribonucleic acid
OCS	oral corticosteroids
PEF	peak expiratory flow
PFM	peak flow meter
PK	pharmacokinetics
PK/PD	pharmacokinetic/pharmacodynamic
PMDA	Pharmaceuticals and Medical Devices Agency
PP	per protocol
Q2W	every 2 weeks
Q4W	every 4 weeks
SABA	short-acting β2 agonist
SAE	serious adverse event
SC	subcutaneous
SID	subject identification

Abbreviation or Specialized Term	Definition
SMC	Safety Monitoring Committee
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
Th2	T helper 2
WPAI-Asthma	Work Productivity and Activity Impairment Questionnaire - Asthma

Study Abstract

TITLE

A Phase 2b, Randomized, Double-blind Study to Evaluate the Efficacy of Tralokinumab in Adults with Uncontrolled, Severe Asthma.

OBJECTIVES

Primary Objective:

To evaluate two subcutaneous (SC) treatment regimens of 300 mg tralokinumab compared with placebo by assessing the effect on asthma exacerbation rate over 52 weeks in adults with uncontrolled, severe asthma requiring high-dose inhaled corticosteroids (ICS) and long-acting β2 agonists (LABA) with or without additional asthma controller medications.

Secondary Objectives:

- To evaluate the safety and tolerability of tralokinumab.
- To evaluate the effect of tralokinumab on pulmonary function: clinic spirometry, including pre- and post-bronchodilator forced expiratory volume in 1 second (FEV_1), forced expiratory volume in 6 seconds (FEV_6), forced vital capacity (FVC), inspiratory capacity (IC); and peak expiratory flow (PEF) and FEV_1 measured at home.
- To evaluate the effect of tralokinumab on Patient Reported Outcomes: Asthma Control Questionnaire (6-item version; ACQ-6) score, health-related quality of life (HRQoL) using Asthma Quality of Life Questionnaire Standardised Version (AQLQ[S]), and EQ-5D.
- To evaluate the effect of tralokinumab on asthma symptoms using the Assessing Symptoms of Moderate-to-severe Asthma (ASMA) diary and use of rescue medication.
- To describe the pharmacokinetics (PK) and immunogenicity of tralokinumab.

Exploratory Objectives:

- To evaluate the effect of tralokinumab on the healthcare resource utilization and productivity using the work productivity and activity impairment (WPAI)-asthma. These data will be reported in the clinical study report.
- To explore the effect of tralokinumab on airway wall thickening using high-resolution computed tomography (HRCT; selected sites only). This is optional for subjects and these data will be reported separately from the clinical study report.
- To explore the relationship between the clinical response to tralokinumab and the presence of peripheral biomarkers detected in blood that may be associated with upregulation of interleukin-13 (IL-13). Biomarkers will include messenger ribonucleic acid and serum proteins. These data will be reported separately from the clinical study report.
- To collect and store deoxyribonucleic acid for future exploratory research into genes/genetic variation that may influence clinical response to tralokinumab. This is optional for subjects and these data will be reported separately from the clinical study report.

STUDY DESIGN

This is a Phase 2b, randomized, double-blind, placebo-controlled, parallel-arm, multicenter study to evaluate the efficacy and safety of two SC treatment regimens of tralokinumab in adult subjects with uncontrolled, severe asthma requiring high-dose ICS and LABA with or without additional controller medications (high-dose ICS defined as a total daily dose > 500 µg fluticasone dry powder inhaler [DPI] or > 440 µg metered dose inhaler [MDI]; GINA, 2009; National Heart, Lung, and Blood Institute, 2007). Approximately 140 sites around the world will participate in the study. At least 390 subjects will be randomized in a 1:1 ratio to one of 2 cohorts

(Cohort 1 or Cohort 2); this includes approximately 65 Japanese subjects from sites in Japan. Within each cohort, subjects will be randomized in a 2:1 ratio to receive tralokinumab (300 mg) or placebo as follows:

- Cohort 1: Tralokinumab 300 mg (n = 130) or Placebo (n = 65) as 2 SC injections every 2 weeks (Q2W) for 50 weeks for a total of 26 doses
- Cohort 2: Tralokinumab 300 mg (n = 130) or Placebo (n = 65) as 2 SC injections Q2W for 12 weeks followed by every 4 weeks (Q4W) for 38 weeks for a total of 16 doses

Subjects will be stratified at screening by the number of asthma exacerbations in the past 12 months (2 versus > 2 but ≤ 6 exacerbations) and by chronic oral corticosteroid (OCS) use (presence versus absence).

A 5-week screening/run-in period (Week -5 to -1 [Day -1]) will precede investigational product administration. Starting at Week -4 (Day -28), subjects will receive a fixed-dose combination product of fluticasone/salmeterol, either as an MDI (230 μg/21 μg) at a dose of 2 inhalations twice per day or as a DPI (500 μg/50 μg) at a dose of one inhalation twice per day. Sites/subjects will be permitted to use either presentation of fluticasone/salmeterol if approved and available for use in their country. If the subject is also taking additional asthma controller medications (including leukotriene modifiers, theophylline, cromones, a secondary ICS, or oral prednisolone ≤ 20 mg/day or equivalent OCS), then these medications should be continued at a stable dose during the screening/run-in period. During the study, subjects may use inhaled reliever therapy (eg, short-acting β2 agonist or short-acting anticholinergic) on an as-required basis as documented in their Personalized Asthma Action Plan.

Eligible subjects who are in the 5-week screening/run-in period at the time 390 subjects have been randomized into the study will also be randomized into the study and followed through completion.

Subjects will continue to receive the same fixed-dose combination product of fluticasone/salmeterol with or without additional asthma controller medications at a stable dose during the treatment period and through Week 53. Subjects who experience an asthma exacerbation during the treatment period will be treated accordingly and will remain in the study.

Subjects will return to the clinic at Week 53 for an assessment of the efficacy endpoints. Subjects will have 3 additional follow-up visits at Weeks 59, 67, and 75. After the Week 53 visit, background medications may be changed as deemed necessary by the investigator.

As part of the study, selected sites will take part in a substudy using HRCT scanning to measure potential airway wall structural changes including airway wall thickness. Sites will be selected on their ability and willingness to carry out the scans. Participation in this substudy is optional for subjects at the selected sites. An adequate number of sites will be identified in order to target recruitment of approximately 40 subjects into each of the 2 cohorts for the HRCT substudy.

Subjects will be in the study for 79 weeks, including a 5-week screening/run-in period (Week -5 to Week -1), a 48- or 50-week treatment period (Weeks 1-51 for Cohort 1 and Weeks 1-49 for Cohort 2), and a 24-week follow-up period (Weeks 51-75).

SUBJECT POPULATION

The subjects in this study will be adults aged 18-75 years with uncontrolled, severe asthma requiring high-dose ICS and LABA with or without additional controller medications.

TREATMENT REGIMEN

At least 390 subjects will be randomized in a 1:1 ratio to one of 2 cohorts. Within each cohort, subjects will be randomized in a 2:1 ratio to receive SC tralokinumab (300 mg) or placebo. Investigational product (tralokinumab or placebo) will be administered as 2 SC injections of 1 mL either Q2W for 50 weeks for a total of 26 doses (Cohort 1) or Q2W for 12 weeks followed by Q4W for 38 weeks for a total of 16 doses (Cohort 2).

Cohort	N Randomized	Treatment Regimen
1	130	300 mg SC tralokinumab Q2W for 50 weeks for a total of 26 doses
	65	Placebo Q2W for 50 weeks for a total of 26 doses
2	130	300 mg SC tralokinumab Q2W for 12 weeks followed by Q4W for 38 weeks for a total of 16 doses
	65	Placebo Q2W for 12 weeks followed by Q4W for 38 weeks for a total of 16 doses

ASSESSMENT OF ENDPOINTS

The primary objective of this study is to evaluate the effect of two SC treatment regimens of 300 mg tralokinumab compared with placebo by assessing the asthma exacerbation rate over 52 weeks in adults with uncontrolled, severe asthma requiring high-dose ICS and LABA with or without additional controller medications. The primary efficacy endpoint is the annual asthma exacerbation rate. The primary endpoint analysis will be conducted based on the intent-to-treat (ITT) population using a Poisson regression model adjusted for overdispersion with treatment group, age, gender, and number of asthma exacerbations in the previous year, and chronic OCS use as potential covariates and the log of number of days in the study as an offset. The primary endpoint will also be analyzed using a negative binomial regression model to assess the robustness with regard to the distributional assumptions. Pairwise comparisons between individual tralokinumab treatment group and combined placebo from Cohorts 1 and 2 will be conducted. Comparison between tralokinumab and placebo from the same cohort will be conducted as secondary analyses. The primary endpoint will also be analyzed using Cochran-Mantel-Haenszel (CMH) row Mean Score Test based on ITT Population, the adjusted number of exacerbations for subjects who withdraw from the study will be calculated using the following equation: [recorded number of exacerbations] / [number of days in the study] × 365.25.

The safety of tralokinumab is a secondary objective of this study, which will be assessed by summarizing treatment-emergent adverse events (AEs) and serious adverse events (SAEs) as well as other safety measurements based on safety population. Treatment-emergent AEs and SAEs will be summarized categorically by system organ class, Medical Dictionary for Regulatory Activities preferred term, severity, and relationship to investigational product from initiation of investigational product through Week 75. Other safety assessments include but not limited to physical examination measurement, vital signs, and routine laboratory assessments. These measurements as well as their changes from baseline will be evaluated at each collection time point. In addition, if warranted, shift tables will be included.

The effect of tralokinumab on pulmonary function as measured by pre- and post bronchodilator FEV_1, FEV_6, FVC, and IC at clinic visits (morning); and PEF and FEV_1 measured at home. Change from baseline in the mean values and percent change from baseline at various timepoints will be summarized using descriptive statistics. Two-sample t-test will be used to compare the changes from baseline and percent changes from baseline in the subject's pulmonary function between the individual tralokinumab treatment group and combined placebo.

Analysis of the secondary endpoints will include the change from baseline in the mean ACQ-6 score, HRQoL evaluated using the AQLQ(S) and EQ-5D. The EQ-5D questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The responses from each dimension and the visual analog scale will be summarized by treatment group and visits. The ASMA Diary is a 13-item questionnaire developed by MedImmune and UBC. Subjects are asked to recall their experience with daytime and nighttime symptom frequency and severity, activity avoidance and limitation, asthma-related stress and fatigue as well as rescue medication use. Each item with be summarized showing change over time compared to baseline scores.

Tralokinumab serum concentrations will be tabulated by treatment group along with descriptive statistics. Serum tralokinumab concentration-time profiles by treatment group will be generated and included in the report. Population modeling may be performed to better characterize the PK of tralokinumab given by SC injection in

asthmatic subjects. The incidence rate of anti-drug antibodies will be reported by tralokinumab treatment group.

Two formal analyses, (Stage 1 analysis and Stage 2 analysis) as well as an interim analysis are planned for the study.

The Stage 1 analysis will be conducted when at least 390 subjects have completed the Week 53 visit. During the Stage 1 analysis, all the efficacy and safety data collected through Week 53 will be analyzed. Study site personnel and the subjects will remain blinded to the treatment assignment for individual subjects until the end of the follow-up period to Week 75. MedImmune will be unblinded at the primary analysis.

The Stage 2 analysis for long-term safety follow-up will be performed after all subjects have completed the study.

The Pharmaceuticals and Medical Devices Agency (PMDA), Japan recommends that Japanese subjects should be included in studies in order to identify inter-ethnic differences in the dose-response relationship early in clinical development. Following discussion with PMDA, the target number of Japanese subjects for inclusion in this study is approximately 65. A subgroup analysis of the Japanese subjects and non-Japanese subjects will be performed.

INTERIM ANALYSIS

One interim analysis is planned for the study and will be conducted after the last non-Japanese subject randomized into the study has completed the Week 39 visit or discontinued prematurely. All data available will be analyzed as part of the interim analysis.

The overall type I error rate (two-sided) will be controlled at the 0.15 level using O'Brien-Fleming alpha spending function based on the actual person-years follow-up observed. For example, if the information fraction at the interim analysis is 88%, then the two-sided type I error rate will be 0.105 for the interim analysis and 0.128 for final analysis, respectively. The interim analysis will have minimal impact on the power of the study at the final analysis, which is estimated to be approximately 78%.

To ensure the blinding of each subject's treatment assignment throughout the study, the interim analysis will be performed by a limited number of sponsor personnel who are not involved in the conduct of the study. Study subjects, site personnel and sponsor personnel directly associated with the conduct of the study will remain blinded to the treatment assignment for individual subjects until the completion of the study.

SAMPLE SIZE AND POWER CALCULATIONS

Sample size calculations have been performed by simulations combined with normal approximation. Simulations assume the data follow exact Poisson distribution. Simulated data have been analyzed using Poisson regression without adjusting for overdispersion.

At least 390 subjects will be randomized in a 1:1 ratio to one of 2 cohorts (Cohorts 1 or Cohort 2). Within each cohort, subjects will be randomized in a 2:1 ratio to receive SC tralokinumab (300 mg) or placebo. The primary analysis will be based on the ITT population.

Fifty-three subjects per treatment arm would be required to detect a 40% reduction in annual asthma exacerbation rate for each tralokinumab treatment group compared to placebo assuming an annual exacerbation rate in placebo group of 1.2 with 80% power and a significance level of 0.1. Sample size was increased to 65 per treatment arm to accommodate overdispersion of 1.2. Recent data suggest that approximately half of asthmatic subjects may have a molecularly distinct subtype of asthma characterized by IL-13-driven inflammation; it is reasonable to hypothesize that these IL-13-positive subjects will have the optimal response to tralokinumab therapy. Therefore the sample size has been increased from 65 to approximately 130 subjects per treatment group to allow for a subanalysis to explore the relationship between the clinical response to tralokinumab and the presence of peripheral blood biomarkers associated with upregulation of IL-13 in the asthmatic lung. In the event that the clinical response is observed only in IL-13-positive subjects, this sample size retains adequate power to detect a difference in the asthma exacerbation rate comparing IL-13-positive tralokinumab treated subjects versus placebo.

The accrual of asthma exacerbations is monitored during the study and blinded estimates of the annual asthma

exacerbation rate in the placebo group are calculated. These estimates are consistently lower than the planned placebo rate of 1.2 exacerbations per year. In order to maintain adequate power to detect a 40% reduction in the annual asthma exacerbation rate for each tralokinumab cohort compared to placebo, the significance level for the data analysis will be raised from two-sided 0.1 to two-sided 0.15.

Sites in Japan will randomize approximately 65 Japanese subjects as part of the overall sample size. In the event that enrollment of the Japanese subjects is significantly delayed, and to ensure a timely Stage 1 analysis, non-Japanese sites may contribute sufficient subjects to reach the sample size required for the Stage 1 analysis (at least 390 subjects). In this event, sites in Japan will be permitted to continue enrollment until such time as approximately 65 Japanese subjects have been enrolled. Subgroup analysis of the Japanese subjects for the Stage 1 analysis will be conducted when all subjects have completed the Week 53 visit.

1 Introduction

1.1 Disease Background

Asthma is a chronic inflammatory disease in the airways characterized by bronchial hyperactivity and reversible limitation of airflow that causes wheezing, shortness of breath, cough, and chest tightness. International treatment guidelines such as Global Initiative for Asthma (GINA; GINA, 2009) recommend inhaled corticosteroids (ICS) as first-line therapy for persistent asthma. For those patients that are symptomatic and on ICS alone, the addition of a long-acting β2-agonist (LABA) is the current treatment of choice. However, there are a number of asthmatic patients who are still symptomatic despite treatment with ICS and LABA combinations (Rabe et al, 2004). Treatment options then include the addition of other controller therapies including leukotriene antagonists, theophylline, and oral glucocorticosteroids. Xolair® (omalizumab) may be suitable for a subgroup of patients with elevated serum immunoglobulin (IgE) levels.

Approximately 5% to 10% of asthma patients have severe asthma, which may be inadequately controlled by ICS and LABA combinations together with additional controller therapies (Brightling et al, 2008). These patients are at risk of asthma exacerbations (Tough et al, 1998; Turner et al, 1998) and have the greatest medical need among the asthmatic population today and represent the greatest economic cost (> 50% of total asthma-related health care costs; Antonicelli et al, 2004; Serra-Batlles et al, 1998; Barnes et al, 1996). Thus, there is a clear medical need for patients with severe asthma who are unable to gain complete asthma control using currently available therapies.

Interleukin-13 (IL-13) is a member of the interleukin family of cytokines and is secreted predominantly by CD4+ T-helper-2 (Th2) cells. Interleukin-13 receptors are expressed on a number of cell types including key cells involved in asthma (Hershey, 2003). There is considerable evidence that IL-13 is a key mediator in the pathogenesis of established asthmatic disease and may have a number of effects (Hershey, 2003; Saha et al, 2008) including:

- The development of airway hyperresponsiveness (AHR) through the recruitment and activation of inflammatory cells (Wardlaw et al, 1988) increased IgE synthesis and consequent mast cell activation (Kaur et al, 2006), caused direct effects on airway smooth muscle cells enhancing cell proliferation, and potentiated bronchoconstriction induced by acetylcholine or histamine (Grunstein et al, 2002; Laporte et al, 2001;

Lee et al, 2001) and through the regulation of secreted molecules, such as nitric oxide, that affect smooth muscle (Doherty et al, 1993).

- Regulating airway inflammation by stimulating the production of the eosinophil chemoattractant C-C motif chemokine ligand-11 (eotaxin-1) and upregulating vascular cell adhesion molecule-1 expression.
- Increasing the numbers of mucus-secreting cells.
- Promoting airway fibrosis in asthma (Wills-Karp et al, 1998).

In animal models, the administration of IL-13 results in the development of features that closely resemble allergic asthma (Wills-Karp et al, 1998). In humans with asthma, raised levels of IL-13 have been found in bronchial biopsies, sputum, and bronchoalveolar lavage (BAL) fluid. Elevated expression of messenger ribonucleic acid (mRNA) encoding IL-13 has been demonstrated in the bronchial mucosa of patients with asthma, regardless of their atopic status, as compared with that in control subjects without asthma matched for atopic status (Humbert et al, 1997). These data are compatible with the hypothesis that IL-13 plays a role in the pathogenesis of both atopic and nonatopic asthma. Furthermore, a positive relationship between raised IL-13 levels and disease severity has been observed (Saha et al, 2008), and genetic studies have indicated that variants of the IL-13 gene may be linked to human disease (Wills-Karp et al, 1998).

A molecularly distinct subtype of asthma characterized by IL-13-driven inflammation has recently been described (Woodruff et al, 2009), which was observed in approximately half of the asthmatic subjects studied. This observation is consistent with the proportion of subjects with severe asthma (both atopic and nonatopic) that have been shown to have IL-13 detectable in their sputum in both published data (Saha et al, 1998) and data available to the sponsor.

Further information on the role of IL-13 in asthma, and a full list of citations, can be found in the Investigator's Brochure for tralokinumab.

1.2 Description of Tralokinumab

Tralokinumab (CAT-354) is briefly described below. Refer to the current Investigator's Brochure for details.

1.2.1 Product Derivation

Tralokinumab is a human recombinant monoclonal antibody (MAb) of the immunoglobulin G4 (IgG4) subclass that specifically binds human IL-13, blocking interactions with the IL-13 receptor. MedImmune has used phage display and recombinant deoxyribonucleic acid (DNA) technologies to isolate a human MAb fragment with specificity for human IL-13 that demonstrated potent in vitro neutralisation of IL-13 activity. Tralokinumab resulted from reformatting the precursor as a human IgG4 isotype (CAT-354) by recombinant DNA technology.

1.2.2 Summary of Nonclinical Experience

In vitro assays have demonstrated that tralokinumab is a potent inhibitor of IL-13-induced effects in a range of cells relevant to asthma. In vivo, in a mouse model of human IL-13-induced lung inflammation and AHR, tralokinumab effectively inhibited inflammatory cell influx into the lung and attenuated AHR to methacholine provocation. Tralokinumab also inhibited antigen-induced pulmonary inflammation and AHR in an experimental model of allergic airway disease in cynomolgus monkeys.

Toxicology studies were conducted in cynomolgus monkeys following single and repeated intravenous (IV) and subcutaneous (SC) doses of tralokinumab. Following multiple IV doses of up to 100 mg/kg/week tralokinumab (longest administration schedule was weekly for 26 weeks), there were no local or systemic dose-limiting toxicities and a no-observable-adverse-effect-level of 100 mg/kg/week was identified. Repeated SC dose studies in cynomolgus monkeys showed no local or systemic effects when administered as 4-weekly SC doses up to 225 mg/injection or as 13-weekly doses up to 300 mg/injection. No adverse effects were noted in a pilot embryo-foetal development toxicity study and in a pre- and post-natal development study following the highest dose tested (100 mg/kg IV).

1.2.3 Summary of Clinical Experience

Six clinical studies have been completed with tralokinumab and are described in the Investigator's Brochure. These include 4 Phase 1 studies (Studies CAT-354-0401, CAT-354-0602, CAT-354-0703, and MI-CP224) and two Phase 2a studies (Studies CAT-354-0603 and MI-CP199).

Study MI-CP199 was a Phase 2a proof of concept study in which tralokinumab (150, 300, or 600 mg) or placebo was administered as a SC injection at 14-day intervals for a total of 7 doses to adult subjects with uncontrolled, moderate-to-severe, persistent asthma. A clinical effect was observed with the addition of SC tralokinumab to standard asthma controller medications in the study. Although the primary endpoint (mean change from baseline in the mean Asthma Control Questionnaire score) of the study was not met, an increase in prebronchodilator forced expiratory volume in 1 second (FEV_1) was observed at the first scheduled visit (2 weeks) after first dose of tralokinumab. At the primary endpoint, Day 92, the mean increase from baseline FEV_1 was 0.063 L (4.3%) in the placebo group versus 0.210 L (12.5%) in the combined tralokinumab treatment group $p = 0.072$. The magnitude of the improvement in FEV_1 in the combined tralokinumab treatment group compared with placebo approximates the minimal important difference of 10% (Reddel et al, 2009). Across the majority of study timepoints, the magnitude of the increase in FEV_1 was similar in the 300 and 600 mg tralokinumab treatment groups, while smaller improvements were observed in the 150 mg tralokinumab treatment group. Of note, the improvement in airflow obstruction in subjects that received tralokinumab was also apparent at Day 169 (12 weeks after the final dose of tralokinumab), suggesting a persistence of the treatment effect on this endpoint. Subgroup analysis of the treatment effect in subjects that received tralokinumab showed that a similar increase in FEV_1 was observed in those subjects whose asthma controller regimen included either high-dose ICS and/or oral corticosteroids (OCS) at baseline compared to the combined tralokinumab treatment group and also that an increase in FEV_1 was observed in both atopic and nonatopic subjects. Treatment with tralokinumab also showed a trend towards greater increase in change from baseline of forced vital capacity (FVC) and clinic measured peak expiratory flow (PEF) in the combined tralokinumab treatment group compared to the changes in the placebo group, although these differences were not statistically significant. A reduction in the requirement for the use of additional short-acting β2 agonist (SABA) was observed in those subjects that received tralokinumab that was consistent with the observed increase in FEV_1.

In Study MI-CP199, a total of 186/194 (95.9%) randomized subjects completed the study and tralokinumab was generally well tolerated. The most common (≥ 5% subjects) treatment-emergent adverse events (AEs) were asthma, headache, and nasopharyngitis. There were no serious adverse events (SAEs) considered related to tralokinumab.

Two treatment-emergent SAEs have been reported in other clinical studies with tralokinumab; one subject who had received one IV dose of tralokinumab at 5 mg/kg

experienced a lower respiratory tract infection, precipitating an exacerbation of asthma (Study CAT-354-0602) that was considered unlikely to be related to investigational product; and one event of acute hypersensitivity reaction was reported in a 30-year-old female subject with a history of asthma and multiple allergies who received an IV infusion of 10 mg/kg tralokinumab (Study CAT-354-0603) that was considered as related to investigational product.

Across all studies with tralokinumab, there was no evidence of anti-drug antibodies (ADA) following either IV or SC administration.

1.3 Research Hypothesis

The hypothesis for the development of tralokinumab is that blockade of IL-13 will result in improved control of asthma. The primary objective of this study is to establish whether the addition of tralokinumab to high-dose ICS and LABA treatment results in a reduction in the rate of asthma exacerbations in subjects with uncontrolled, severe asthma (high-dose ICS defined as a total daily dose > 500 µg fluticasone dry powder inhaler [DPI] or > 440 µg metered dose inhaler [MDI]; GINA, 2009; National Heart, Lung, and Blood Institute, 2007). In Study MI-CP199 increases in prebronchodilator FEV_1 were observed following the addition of tralokinumab to standard asthma controller medications; since low prebronchodilator FEV_1 has been identified as a strong independent predictor of subsequent asthma exacerbations, it is plausible that the addition of tralokinumab will reduce the rate of asthma exacerbations in this population (Kitch et al, 2004; Reddel et al, 2009).

1.4 Rationale for Study Conduct

The Phase 2a study MI-CP199 provided evidence of a reduction in airflow obstruction following the addition of SC tralokinumab to standard asthma controller medications both at Day 92 (end of treatment period) and Day 169 (12 weeks after the final dose of tralokinumab). Both the 300 and 600 mg doses of tralokinumab resulted in comparable effects on FEV_1 that were greater than those observed with the 150 mg dose. No treatment effects were observed with tralokinumab at any dose on asthma symptoms and asthma related quality of life.

The aim of the current study is to evaluate the effect of multiple SC doses of 300 mg tralokinumab on relevant aspects of asthma control including the annual asthma exacerbation

rate, lung function, asthma symptoms, and health-related quality of life (HRQoL) compared with placebo over a longer treatment period of 52 weeks. Asthma exacerbations constitute a significant risk to the health of subjects with asthma and the management of acute exacerbations generates significant cost to health care systems. Recent treatment guidelines have identified the reduction of the frequency of exacerbations as an important management goal (GINA, 2009; Lane et al, 2006). This study has therefore been designed to establish whether the addition of tralokinumab to currently available standard asthma controller medications can reduce the rate of asthma exacerbations in subjects at risk of these events as the primary endpoint.

Following an initial 12-week period of dosing with investigational product every 2 weeks (Q2W), 2 'maintenance' dosing regimens will be evaluated, with dosing Q2W or every 4 weeks (Q4W) through to the primary endpoint at Week 53. Subjects will be followed up for a further 22 weeks after the primary endpoint assessment to study the persistence or decline of any changes in asthma control after the cessation of treatment with investigational product.

1.5 Benefit-Risk and Ethical Assessment

There is an unmet medical need for new therapies for use in subjects unable to gain asthma control using standard asthma controller medications. In Study MI-CP199, treatment with tralokinumab showed evidence of a clinical effect compared with placebo (see Section 1.2.3), and therefore further study of tralokinumab as a potential therapeutic asthma controller therapy is warranted.

In clinical studies completed to date, tralokinumab was generally well tolerated. A number of possible risks have been identified that are described in the current Investigator Brochure and measures are in place in this study to protect participating subjects as follows:

- Subjects will be closely monitored during the course of the study with clinic visits Q2W during the treatment period and daily diary recordings of FEV_1, PEF, asthma symptoms, and use of reliever medication.
- One acute hypersensitivity reaction, characterized by increased wheezing, shortness of breath, and facial pruritus, was reported in an asthmatic subject following the first IV infusion of tralokinumab (10 mg/kg) in Study CAT-354-0603. However, in Study MI-CP199, no hypersensitivity reactions were reported following repeat SC dosing. As a precautionary measure in this study, subjects will be monitored for immediate drug reactions; vital signs will be taken immediately after administration of investigational product and at least every 30 minutes thereafter. For the first 4 doses of investigational product, subjects will remain at site for a minimum of 2 hours or

until stable, whichever is later. For the fifth and subsequent doses of investigational product, subjects will remain at site for a minimum of 1 hour or until stable, whichever is later. Discharge from site will be determined by the investigator. Medical equipment to treat acute anaphylactic reactions will be immediately available in this study, and study personnel will be trained to recognize and treat anaphylaxis (Appendix 2).

- Neutralization of IL-13 might theoretically cause a worsening of parasitic infestation, in particular, prevention of expulsion of gastrointestinal worms (Bell, 1996) and therefore, subjects either with untreated systemic helminth parasitic infestations or at significant increased risk of parasitic infestation will be excluded.
- A recent chest x-ray or computed tomography (CT) scan is required to exclude the presence of concomitant respiratory pathology including tuberculosis (TB).
- No evidence of formation of ADAs has been detected in previous clinical studies; however, subjects will be monitored both for clinical manifestations that may be associated with the formation of specific antibodies to tralokinumab and for the presence of such antibodies.

The information gained from this study will have significant value in determining whether tralokinumab has the potential to be developed as a controller therapy for uncontrolled, severe asthma. Previous clinical experience with tralokinumab shows no major safety or tolerability concerns and appropriate measures have been instituted in this study to protect subjects from possible risks that have been identified and to monitor subjects closely. Hence, the current risk/benefit ratio is favorable and justifies the administration of tralokinumab in this study.

2 Study Objectives

2.1 Primary Objective

To evaluate two SC treatment regimens of 300 mg tralokinumab compared with placebo by assessing the effect on asthma exacerbation rate over 52 weeks in adults with uncontrolled, severe asthma requiring high-dose ICS and LABA with or without additional asthma controller medications.

2.2 Secondary Objectives

1) To evaluate the safety and tolerability of tralokinumab.

2) To evaluate the effect of tralokinumab on pulmonary function: clinic spirometry, including pre- and post-bronchodilator FEV_1, forced expiratory volume in 6 seconds (FEV_6), FVC, inspiratory capacity (IC); and PEF and FEV_1 measured at home.

3) To evaluate the effect of tralokinumab on Patient Reported Outcomes: Asthma Control Questionnaire (6-item version; ACQ-6) score, HRQoL using Asthma Quality of Life Questionnaire Standardised Version (AQLQ[S]), and EQ-5D.

4) To evaluate the effect of tralokinumab on asthma symptoms using the Assessing Symptoms of Moderate-to-severe Asthma (ASMA) diary and use of rescue medication.

5) To describe the pharmacokinetics (PK) and immunogenicity of tralokinumab.

2.3 Exploratory Objectives

1) To evaluate the effect of tralokinumab on the healthcare resource utilization and productivity using the work productivity and activity impairment (WPAI)-asthma. These data will be reported in the clinical study report.

2) To explore the effect of tralokinumab on airway wall thickening using high-resolution computed tomography (HRCT; selected sites only). This is optional for subjects and these data will be reported separately from the clinical study report.

3) To explore the relationship between the clinical response to tralokinumab and the presence of peripheral biomarkers detected in blood that may be associated with upregulation of IL-13. Biomarkers will include mRNA and serum proteins. These data will be reported separately from the clinical study report.

4) To collect and store DNA for future exploratory research into genes/genetic variation that may influence clinical response to tralokinumab. This is optional for subjects and these data will be reported separately from the clinical study report.

3 Study Design

3.1 Overview of Study Design

This is a Phase 2b, randomized, double-blind, placebo-controlled, parallel-arm, multicenter study to evaluate the efficacy and safety of two SC treatment regimens of tralokinumab in adult subjects with uncontrolled, severe asthma requiring high-dose ICS and LABA with or without additional controller medications (high-dose ICS defined as a total daily dose > 500 µg fluticasone DPI or > 440 µg MDI; GINA, 2009; National Heart, Lung, and Blood Institute, 2007). Approximately 140 sites around the world will participate in the study. At least 390 subjects will be randomized in a 1:1 ratio to one of 2 cohorts (Cohort 1 or Cohort 2); this includes approximately 65 subjects from sites in Japan. Within each cohort,

subjects will be randomized in a 2:1 ratio to receive tralokinumab (300 mg) or placebo as follows:

Cohort 1: Tralokinumab 300 mg (n = 130) or Placebo (n = 65) as 2 SC injections Q2W for 50 weeks for a total of 26 doses

Cohort 2: Tralokinumab 300 mg (n = 130) or Placebo (n = 65) as 2 SC injections Q2W for 12 weeks followed by Q4W for 38 weeks for a total of 16 doses

Subjects will be stratified at screening by the number of asthma exacerbations in the past 12 months (2 versus > 2 but ≤ 6 exacerbations) and by chronic OCS use (presence versus absence).

A 5-week screening/run-in period (Week -5 to -1 [Day -1]) will precede investigational product administration. Starting at Week -4 (Day -28), subjects will receive a fixed-dose combination product of fluticasone/salmeterol, either as an MDI (230 µg/21 µg) at a dose of 2 inhalations twice per day or as a DPI (500 µg/50 µg) at a dose of one inhalation twice per day. Sites/subjects will be permitted to use either presentation of fluticasone/salmeterol if approved and available for use in their country. If the subject is also taking additional asthma controller medications (including leukotriene modifiers, theophylline, cromones, a secondary ICS, or oral prednisolone ≤ 20 mg/day or equivalent OCS), then these medications should be continued at a stable dose during the screening/run-in period. During the study, subjects may use inhaled reliever therapy (eg, SABA or short-acting anticholinergic) on an as-required basis as documented in their Personalized Asthma Action Plan (see Section 4.5.2.1).

Eligible subjects who are in the 5-week screening/run-in period at the time 390 subjects have been randomized into the study will also be randomized into the study and followed through completion.

Subjects will continue to receive the same fixed-dose combination product of fluticasone/salmeterol with or without additional asthma controller medications at a stable dose during the treatment period and through Week 53. Subjects who experience an asthma exacerbation during the treatment period will be treated accordingly and will remain in the study.

Subjects will return to the clinic at Week 53 for an assessment of the efficacy endpoints. Subjects will have 3 additional follow-up visits at Weeks 59, 67, and 75. After the Week 53 visit, background medications may be changed as deemed necessary by the investigator.

As part of the study, selected sites will take part in a substudy using HRCT scanning to measure potential airway wall structural changes including airway wall thickness. Sites will be selected on their ability and willingness to carry out the scans. Participation in this substudy is optional for subjects at the selected sites. An adequate number of sites will be identified in order to target recruitment of approximately 40 subjects into each of the 2 cohorts for the HRCT substudy.

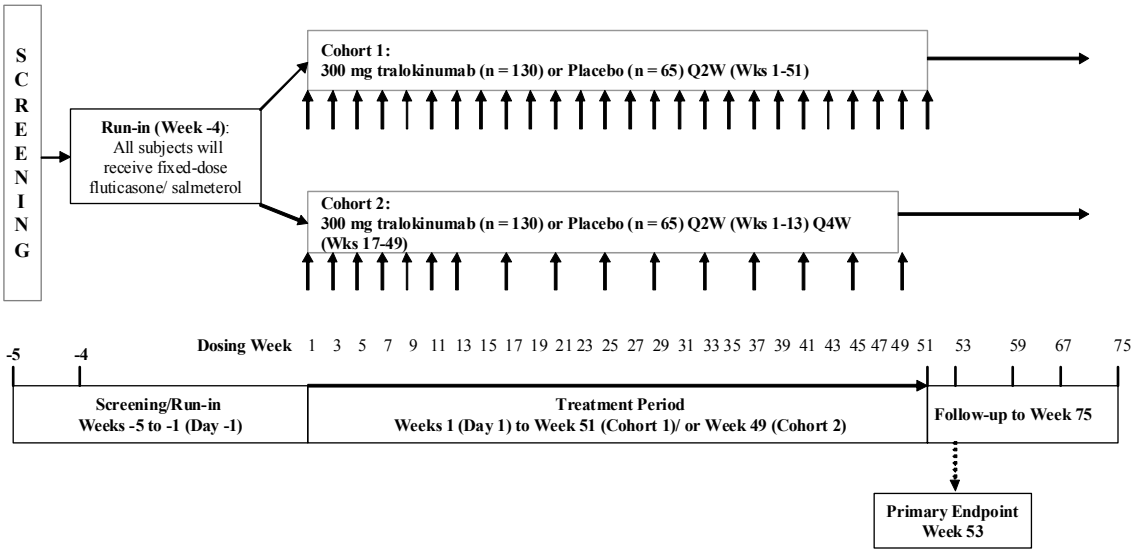

Figure 3.1-1 Study Flow Diagram

Q2W = every 2 weeks; Q4W = every 4 weeks; Wks = Weeks

The endpoints to be measured in this study are described in Section 7.3.

3.2 Estimated Duration of Subject Participation

Subjects will be in the study for 79 weeks, including a 5-week screening/run-in period (Week -5 to Week -1), a 48- or 50-week treatment period (Weeks 1-51 for Cohort 1 and Weeks 1-49 for Cohort 2), and a 24-week follow-up period (Weeks 51-75).

3.3 Study-stopping Criteria

If the sponsor receives a report of an event consistent with any of the study-stopping criteria, the medical monitor will immediately assess the event by gathering all available information, including where possible, direct telephone contact with the reporter. If the assessment confirms the event as a study-stopping event, further dosing will be stopped and no additional subjects will be entered into the study. Notification of the event, its assessment, and whether

or not the study has been interrupted must be made to the MedImmune Safety Monitoring Committee (SMC) by the medical monitor within 1 business day of the receipt of the initial report by the sponsor.

1) Death in any subject in which the cause of death is assessed as related to tralokinumab
2) Confirmed immune complex disease in a subject treated with tralokinumab. A definition of immune complex disease is provided in Appendix 4
3) Events that in the opinion of the medical monitor and the MedImmune SMC contraindicate further dosing of additional subjects

If the study is interrupted, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted to determine whether dosing should be resumed, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the MedImmune SMC is required for resumption of the study in the event that the study is interrupted following one of the above-listed events. Where applicable, regulatory authorities and Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any actions taken with the study.

Any subjects who have already received investigational product and are currently in the study at the time study stopping criteria are met will continue to be followed by the investigator for safety.

Withdrawal criteria for individual subjects are provided in Section 4.2.3.

3.4 Rationale for Study Design, Doses, and Control Groups

3.4.1 Study Rationale and Choice of Study Population

Evidence of a clinical effect following the addition of tralokinumab to standard asthma controller medications over a 12-week period was observed in subjects with uncontrolled, moderate-to-severe persistent asthma in Study MI-CP199. This study is designed to more fully characterize the efficacy, safety, and tolerability of SC tralokinumab when dosed over a period of 52 weeks in a more severe subject population.

A population of severe asthmatic subjects that, despite receiving high-dose ICS (GINA, 2009) and LABA, continue to have uncontrolled (partially or poorly-controlled) asthma are at risk of severe asthma exacerbations (Bousquet et al, 2010) and therefore have a significant unmet need requiring novel asthma controller therapies. Interleukin-13 overexpression in

sputum and bronchial biopsy specimens is a feature of severe asthma (Saha et al, 2008). Blockade of IL-13 with tralokinumab in subjects with severe asthma will establish whether the addition of tralokinumab to high-dose ICS and LABA treatment results in reduction in the rate of asthma exacerbations and improved asthma control.

The Pharmaceuticals and Medical Devices Agency (PMDA), Japan recommends that Japanese subjects should be included in studies in order to identify inter-ethnic differences in the dose-response relationship early in clinical development. Following discussion with PMDA, the target number of Japanese subjects for inclusion in this study is approximately 65. Subgroup analysis for Japanese population will be performed.

3.4.2 Justification of Study Design

The study will be randomized, placebo-controlled, and double-blind to ensure a robust design and minimize bias.

Tralokinumab is being developed as an asthma controller treatment that would be expected to be dosed over extended periods of time; therefore a treatment period of 50 weeks is considered an appropriate duration given that long-term suppression of IL-13 is expected to be required in order to achieve the maximum clinical benefit. The duration of this study is appropriate to ensure that adequate numbers of exacerbation events are observed during the study in order to determine the treatment effect on the primary endpoint.

3.4.3 Justification for Primary and Secondary Endpoints

Tralokinumab is being developed as a controller therapy for subjects with uncontrolled, severe asthma with the aim to achieve and maintain asthma control for prolonged periods. The GINA Guideline (GINA, 2009) recommends that the assessment of asthma control should not only include the control of clinical manifestations (symptoms, sleep disturbance, limitation of daily activity, impaired lung function, and use of rescue medication) but also the control of expected future risk including the incidence of asthma exacerbations.

Asthma exacerbations are important because they constitute the greatest risk to patients, are a cause of anxiety to patients and their families, result in the greatest stress on healthcare providers, and generate the greatest cost to the health care systems (Lane et al, 2006). It is therefore important to establish whether the use of tralokinumab is associated with a

reduction in the annual asthma exacerbation rate versus placebo; this endpoint has therefore been selected as the primary efficacy variable.

The secondary endpoints include other established measures of asthma control (pulmonary function and asthma symptoms) and quality of life, which together with the safety and tolerability of tralokinumab will be critical in establishing its potential clinical utility. The endpoints chosen for this study will therefore provide the opportunity to assess the impact of tralokinumab on these different aspects of asthma control.

3.4.4 Dose Justification and Duration of Treatment

The selection of 300 mg tralokinumab dose for this study is supported both by theoretical pharmacokinetic/pharmacodynamic (PK/PD) modeling and by observations from Study MI-CP199. The PK/PD model describes the bimolecular interaction of tralokinumab with IL-13 in serum and sputum, with partitioning of the antibody, antigen, and complex between the serum and sputum compartments. The model predicts that administration of 300 mg SC tralokinumab Q2W will achieve a > 90% reduction in free IL-13 concentrations in sputum. At least 90% suppression of sputum IL-13 is desired because many cytokines can elicit signaling with receptor occupancies of less than 10%. Given that baseline levels of IL-13 are generally below the receptor dissociation constant, a 90% reduction in IL-13 is expected to reduce receptor occupancy to less than 5%. This prediction is supported by the data from Study MI-CP199 that shows that FEV_1 increased in subjects receiving 300 mg tralokinumab SC Q2W.

Following an initial 12-week period of Q2W dosing, 2 tralokinumab ‘maintenance’ dose frequencies will be evaluated: Q2W, which is the same frequency that provided evidence of clinical effect in Study MI-CP199; and Q4W, which has been included since improvements from baseline in FEV_1 continued to be observed for up to 12 weeks after the last dose of tralokinumab suggesting that dosing less frequently than Q2W may be adequate to realize clinical benefits of IL-13 blockade.

4 Study Procedures

4.1 Subject Participation and Identification

Study participation begins once written informed consent is obtained (see Section 10.3 for details). Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice/web response system, IXRS), and the screening evaluations can begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria), including the reason(s) for screening failure.

4.2 Subject Selection and Withdrawal

The subjects in this study will be adults aged 18-75 years with uncontrolled, severe asthma requiring high-dose ICS and LABA with or without additional controller medications.

The investigator (physician) or qualified designee will discuss the study with a subject who is considered a potential candidate for the study and provide the subject with the study-specific informed consent forms (ICFs) approved by the IRB/IEC. The investigator or designee will address any questions and/or concerns that the subject may have and, if there is continued interest, will secure written informed consent for participation in the study. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act [HIPAA] authorization in the USA, European Union [EU] Data Privacy Directive authorization in the EU), will be obtained prior to conducting any protocol-specific procedures, including screening evaluations. See Section 10.3 for additional details concerning informed consent.

4.2.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1) Age 18-75 years of age at the time of screening (Visit 1).

2) Written informed consent and any locally required authorization (eg, HIPAA in the USA, EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.

3) Body mass index (BMI) between 16-40 kg/m^2 at Visit 1.

4) Documented physician-diagnosed asthma for at least 12 months prior to Visit 1 and EITHER

- Proof of postbronchodilator reversibility of $FEV_1 \geq 12\%$ and ≥ 200 mL to a SABA documented within 36 months prior to Visit 1; OR
- Proof of a positive response to a methacholine ($PC_{20} \leq 8$ mg/mL), histamine or mannitol challenge documented within 36 months prior to Visit 1; OR
- A postbronchodilator increase in $FEV_1 \geq 12\%$ and ≥ 200 mL at Visit 1. If this increase is not observed at Visit 1 the subject may undergo repeat testing at Visit 2.

5) Subjects must have received an asthma controller regimen consistent with that described at Step 4 or 5 of the GINA guidelines (GINA, 2009) for at least 6 of the 12 months prior to Visit 1 and must have used physician prescribed high-dose ICS in combination with LABA for at least 30 days prior to Visit 1 (high-dose ICS defined as a total daily dose > 500 µg fluticasone DPI or > 440 µg MDI, or equivalent; see Appendix 2 for acceptable doses of ICS).

6) For subjects receiving an alternative combination of ICS/LABA prior to Visit 1, a willingness to switch to fluticasone/salmeterol either as a DPI at a dose of 500/50 µg, one inhalation twice per day, or as an MDI at a dose of 230 µg/21 µg, 2 inhalations twice per day, once eligibility has been confirmed at Visit 2.

7) Where applicable, the dose of other asthma controller medications (leukotriene modifiers, theophylline, secondary ICS, OCS, or cromones) must have been stable for at least 30 days prior to Visit 1.

8) Subjects must have a history of at least 2 but no more than 6 documented asthma exacerbation events within the 12 months prior to Visit 1. The 12 month period starts from 30 days prior to Visit 1 (see exclusion criterion 13). To qualify as an exacerbation event, administration of a burst of systemic corticosteroids for at least 3 consecutive days must have been required for the treatment of the asthma exacerbation. At least one asthma exacerbation must have occurred while the subject was receiving an asthma controller regimen consistent with that described at Step 4 or 5 of the GINA guidelines (GINA, 2009).

9) At both Visits 1 and 4, subjects must have at least one of the following; a morning prebronchodilator FEV_1 value of between 40% and 80% predicted or an ACQ-6 score for the preceding week of ≥ 1.5.

10) A chest x-ray taken during the screening period or within the 12 months before Visit 1 that, according to the investigator, is normal for an asthmatic subject and excludes

significant alternative respiratory disease. (Other appropriate lung imaging methods performed within the 12 months before Visit 1 are acceptable; eg, a chest CT scan.)

11) Females of childbearing potential who are sexually active with a nonsterilized male partner must use highly effective contraception from screening, and must agree to continue using such precautions through Week 75 of the study. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

- Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table 4.2.1-1.

12) Nonsterilized males or sterilized males who are ≤ 1 year post-vasectomy who are sexually active with a female partner of childbearing potential must use a highly effective method of contraception (see Table 4.2.1-1) from Day 1 through Week 75.

Table 4.2.1-1 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Male condom plus spermicide • Copper T intrauterine device	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch • Mirena® (Levonorgesterel intrauterine device/system)

13) Ability and willingness to complete the study.

14) Ability to read and write and use the electronic devices required for the study.

15) Assessing Symptoms of Moderate-to-severe Asthma (ASMA) diary entries on the ePRO device must have been completed for at least 8 (any 8) of the last 10 days of the screening/run-in period.

4.2.2 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1) Employee of the clinical study site or any other individuals directly involved with the conduct of the study, or immediate family members of such individuals.

2) Pregnant or breastfeeding women.

3) Individuals who are legally institutionalized.

4) Subjects unable to demonstrate acceptable inhaler and peak flow meter/spirometry techniques as judged by the investigator.

5) Any concomitant respiratory disease that in the opinion of the investigator and/or medical monitor will interfere with the evaluation of the investigational product (eg, chronic obstructive pulmonary disease [COPD] or idiopathic pulmonary fibrosis).

6) Concurrent enrollment in another clinical study where the subject is receiving an investigational product.

7) Previous receipt of tralokinumab.

8) Receipt of any marketed or investigational biologic agent within 4 months or 5 half-lives prior to Visit 1, whichever is longer

9) Receipt of any investigational nonbiologic agent within 3 months or 5 half-lives prior to Visit 1, whichever is longer

10) Subjects who have received a live attenuated vaccine within 4 weeks prior to Visit 1.

11) Use of systemic immunosuppressive medication (eg, methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine, intramuscular long-acting corticosteroid, and oral prednisolone at a dose greater than 20 mg or equivalent OCS) within 3 months prior to Visit 1.

12) Current use of any excluded medications listed in Section 4.6.2

13) Occurrence of an asthma exacerbation event requiring a burst of systemic corticosteroids from 30 days prior to Visit 1, up to and including Visit 4.

14) Known history of allergy or reaction to any component of the investigational product formulation or history of anaphylaxis following any biologic therapy.

15) Known exposure to inhaled occupational agents or fumes with an established diagnosis of occupational asthma.

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

17) Previous medical history or evidence of an uncontrolled intercurrent illness that in the opinion of the investigator and/or medical monitor may compromise the safety of the subject in the study or interfere with evaluation of the investigational product or reduce the subject's ability to participate in the study.

18) Any clinically relevant abnormal findings in physical examination, electrocardiogram (ECG), vital signs, hematology, clinical chemistry, or urinalysis during screening/run-in period, which in the opinion of the investigator or medical monitor may compromise the safety of the subject in the study or interfere with evaluation of the investigational product or reduce the subject's ability to participate in the study.

19) Evidence of active liver disease, including jaundice or aspartate transaminase, alanine transaminase, or alkaline phosphatase greater than twice the upper limit of normal.

20) History of a clinically significant infection (eg, requiring antibiotics or antiviral medications) from 30 days prior to Visit 1, up to and including Visit 4.

21) Subjects who in the opinion of the investigator have evidence of active TB, either treated or untreated, or latent TB without completion of an appropriate course of treatment or appropriate ongoing prophylactic treatment. Evaluation will be according to the local standard of care as determined by local guidelines and may consist of history and physical examinations, chest x-ray, and/or TB test (eg, purified protein derivative or QuantiFeron test).

22) A history of an untreated systemic helminth parasitic infestation; diagnosis of a helminth parasitic infestation within 6 months prior to Visit 1; history of living with a person known to have had a helminth parasitic infestation within 12 months prior to Visit 1.

23) History of chronic alcohol or drug abuse within 12 months of Visit 1, or any condition associated with poor compliance as judged by the investigator.

24) History of any known primary immunodeficiency disorder excluding asymptomatic selective immunoglobulin A or immunoglobulin G (IgG) subclass deficiency.

25) History of cancer, except for basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy ≥ 12 months prior to screening or other malignancies treated with apparent success with curative therapy ≥ 5 years prior to screening.

26) Positive hepatitis B surface antigen or hepatitis C virus antibody serology. Subjects with a history of hepatitis B vaccination without history of hepatitis B are allowed to enrol.

27) A positive human immunodeficiency virus (HIV) test at screening or subject taking antiretroviral medications, as determined by medical history and/or subject's verbal report.

28) Major surgery within 8 weeks prior to Visit 1, or planned in-patient surgery or hospitalisation during the study period.

4.2.3 Withdrawal Criteria

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1) Withdrawal of consent or lost to follow-up

2) Adverse event that, in the opinion of the investigator and/or medical monitor requires early withdrawal as continued participation imposes an unnecessary risk to the subject

3) Pregnancy

4) Anaphylactic reaction to the investigational product (see Appendix 4)

5) Intensive care unit admission for asthma-related event

6) Requirement for omalizumab use

Withdrawal of consent: If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

Lost to follow-up: Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed (as defined in Section 4.8) such that there is insufficient information to determine the subject's status at that time.

- Note: Subjects refusing to return to the site or to continue participation in the study should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and any evaluations should resume according to the protocol.

Permanent discontinuation of investigational product: Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, pregnancy, other; see Section 6.4.3.2 for handling of pregnancies), will be identified as having permanently discontinued treatment. Subjects who permanently discontinue treatment may either be considered to have completed the study or not to have completed the study (see Section 4.7). These subjects should undertake follow-up Visits 30-33, inclusive, and will be followed for safety per Section 6.4 unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study.

4.2.4 Replacement of Subjects

Subjects randomized in error because they did not meet major study eligibility criteria will be reviewed by the medical monitor. Subjects who are withdrawn as a result may be replaced.

4.3 Treatment Assignment

An IXRS will be used for randomization to a cohort and assignment of blinded investigational product kit numbers. A subject is considered randomized into the study when the investigator or designee notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of blinded investigational product kit numbers to the subject.

Subjects will be randomized in a 1:1 ratio to one of 2 cohorts. Within each cohort, subjects will be randomized in a ratio of 2:1 to receive SC tralokinumab (300 mg) or placebo. Subjects will be stratified at screening by both by the number of asthma exacerbations in the past year (2 versus > 2 but ≤ 6 exacerbations) and by chronic OCS use (presence versus absence).

The procedure for using IXRS for randomization is as follows:

- The investigator or designee confirms that written informed consent has been obtained and that the subject has met all eligibility criteria.
- The investigator or designee calls or logs onto the IXRS and provides the SID and subject's baseline characteristic(s) used to verify that it is the same subject.
- The IXRS assigns a cohort and investigational product kit number to the subject.
- Confirmation of this information is sent to the unblinded investigational product manager at the site who dispenses the investigational product to the unblinded team member who will administer investigational product to the subject, and records the appropriate information in the pharmacy record and investigational product accountability log

Investigational product (tralokinumab or placebo) must be administered the same day the investigational product is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified *immediately*.

Eligible subjects who are in the 5-week screening/run-in period at the time 390 subjects have been randomized into the study will also be randomized into the study and followed through to completion.

4.4 Blinding

This is a double-blind study in which tralokinumab and placebo are visually distinct from one another. Neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Conference on Harmonisation [ICH] E9). Since tralokinumab and placebo are visually distinct, investigational product will be handled by an unblinded investigational product manager at the site and will be administered by an unblinded study team member who will not be involved in the management of study subjects. (These could be the same person.) An independent investigational product monitor will also be unblinded to perform

investigational product accountability. In the event that the treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, or needs to be known to treat an individual subject for an AE, the sponsor must be notified *immediately* by the investigator and if possible, before unblinding.

Two formal analyses, Stage 1 analysis and Stage 2 analysis, will performed for the study. The Stage 1 analysis will be conducted after the last subject has completed the Week 53 visit. During the Stage 1 analysis, all the efficacy and safety data collected through Week 53 will be analyzed. Study site personnel and the subjects will remain blinded to the treatment assignment for individual subjects until the end of the follow-up period to Week 75. MedImmune will be unblinded at the primary analysis.

The Stage 2 analysis for long-term safety follow-up will be performed after all subjects have completed the study.

4.4.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Prior to unblinding the investigational product allocation for an individual subject, the investigator must first attempt to contact the medical monitor to discuss the medical emergency and the reason for wanting to unblind. Instructions for unblinding an individual subject's investigational product allocation are contained in the IXRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this is the case, the investigational product allocation should not be unblinded.

4.4.2 Unblinding for Interim Analysis Purposes

An interim analysis is planned for this study as described in Section 7.4. To ensure the blinding of each subject's treatment assignment throughout the study, the interim analysis will be performed by a limited number of sponsor personnel who are not involved in the conduct of the study. Study subjects, site personnel, and sponsor personnel directly associated with the conduct of the study will remain blinded to the treatment assignment for individual subjects until the completion of the study. Additional details will be documented in a separate unblinding plan.

4.5 Study Medications

4.5.1 Investigational Products

MedImmune will provide the investigators with investigational product (Table 4.5.1-1) using designated distribution centers. The sponsor will provide the investigator(s) with adequate stock quantities of investigational product and the stock levels will be maintained via the IXRS as vials are used.

Table 4.5.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Tralokinumab (CAT-354)	MedImmune	Formulated at a nominal concentration of 150 mg/mL [redacted] See Table 4.5.1-2 for full list of excipients.
Placebo	MedImmune	Placebo contains the same excipients, in the same concentration only lacking tralokinumab

Table 4.5.1-2 Tralokinumab (CAT-354) Composition

Ingredient	Concentration	Unit Formula per 150 mg Vial (nominal)
Active Ingredient		
CAT-354	150 mg/mL	150 mg
Other Ingredients		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Investigational product (tralokinumab and placebo) is filled into 3 cc glass vials and will be stored at 2-8°C in a secure area with restricted access. Materials Safety Data Sheets will be provided in the Investigational Product Manual detailing procedures required for the safe handling of the investigational product.

Investigational product will be supplied to the site as kits containing one vial per carton. Both the vial and carton will be labeled in accordance with local regulatory requirements and will contain a unique individual kit number.

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All used/unused investigational product will be disposed of locally upon authorization by MedImmune (refer to the Investigational Product Manual provided by MedImmune for contact information and specific shipping instructions).

Details regarding supplies, dose preparation, process for reporting product complaints, and accountability for the investigational product will be provided in the Investigational Product Manual supplied to the sites.

4.5.2 Other Study Medications

4.5.2.1 Background Medication

All subjects will receive a fixed-dose combination product of fluticasone/salmeterol from Week -4 through Week 53. Two preparations/doses of fluticasone/salmeterol are acceptable:

- Fluticasone/salmeterol MDI; 230 μg/21 μg, 2 inhalations twice per day; or
- Fluticasone/salmeterol as a DPI; 500 μg/50 μg, one inhalation twice per day.

Fluticasone/salmeterol will be sourced locally by site.

If at Week -4 the subject is also taking additional asthma controller medications (including leukotriene modifiers, theophylline, cromones, a secondary ICS, or oral prednisolone ≤ 20 mg/day or equivalent OCS), then these medications should be continued at a stable dose during the run-in period and to Week 53.

The principal aim of this study is to establish the treatment effect of tralokinumab as an 'add-on' therapy; therefore, it is highly desirable that background asthma controller medications are maintained at a stable dose from Week -4 through Week 53, in order to prevent any independent confounding of that treatment effect. However, if the investigator considers a permanent change to background medications between Weeks -4 and Week 53 to be necessary, where possible the change should be discussed with the sponsor's medical

monitor and must be noted in the case report form (CRF). The subject may remain in the study unless the addition of omalizumab is required, in which case the subject must be withdrawn.

Between Week 53 and Week 75, the investigator may change the dose of fluticasone/salmeterol or any additional asthma controller medications per clinical judgment and any changes should be noted in the CRF.

During the study, subjects may use an inhaled SABA or an inhaled short-acting anticholinergic on an as-required basis as a reliever medication as documented in their Personalized Asthma Action Plan.

4.5.2.2 Rescue Medication

Rescue medication will be required in the event of worsening asthma symptoms.

Subjects are expected to use inhaled SABA or an inhaled short-acting anticholinergic as a first-line treatment. If asthma symptoms do not resolve, subjects should contact the investigator (or their healthcare provider) who will manage the subject according to their clinical judgement. Additional outpatient treatment may be required, eg, short-term courses of additional asthma controller medications (up to a maximum of 14 days of continuous treatment), an OCS burst or, in the event of a marked deterioration, hospitalization/emergency room treatment may be necessary. All treatments administered should be noted in the CRF.

4.5.3 Treatment Regimen

At least 390 subjects will be randomized in a 1:1 ratio to one of 2 cohorts. Within each cohort, subjects will be randomized in a 2:1 ratio to receive SC tralokinumab (300 mg) or placebo. Investigational product (tralokinumab or placebo) will be administered as 2 SC injections of 1 mL either Q2W for 50 weeks for a total of 26 doses (Cohort 1) or Q2W for 12 weeks followed by Q4W for 38 weeks for a total of 16 doses (Cohort 2).

Table 4.5.3-1 Treatment Regimen

Cohort	N Randomized	Treatment Regimen
1	130	300 mg SC tralokinumab Q2W for 50 weeks for a total of 26 doses
	65	Placebo Q2W for 50 weeks for a total of 26 doses
2	130	300 mg SC tralokinumab Q2W for 12 weeks followed by Q4W for 38 weeks for a total of 16 doses
	65	Placebo Q2W for 12 weeks followed by Q4W for 38 weeks for a total of 16 doses

N = number; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous

4.5.4 Treatment Administration

The first day of dosing is considered Day 1 (Week 1).

The investigational product will be administered by SC injection. An unblinded qualified designee, who will not be involved in the management of the subjects, will inject the investigational product into the SC tissue of the anterior thigh or abdomen.

Two injections (150 mg per injection) are required in order to administer tralokinumab at the required dose of 300 mg. Therefore at each administration (tralokinumab or placebo) 2 separate injection sites on the anterior thigh or abdomen at least 3 cm apart should be used. Injection sites should be rotated at each visit. The time of the first SC injection will be recorded for each subject.

The investigational product will be administered via a 27-gauge 1/2-inch needle. The person administering the dose will wipe the skin surface of the 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 investigational product 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.

4.5.5 Monitoring of Dose Administration

Vital signs (blood pressure, temperature, pulse rate, and respiration rate) will be obtained before investigational product administration on all treatment visits. After investigational product administration, subjects will be monitored for immediate drug reactions; vital signs

will be taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter. For the first 4 doses of investigational product, subjects will remain at site for a minimum of 2 hours or until stable, whichever is later. For the fifth and subsequent doses of investigational product, subjects will remain at site for a minimum of 1 hour or until stable, whichever is later. Discharge from site will be determined by the investigator.

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 (eg, IgG and immune complex mediated) and nonimmunologic (Johansson et al, 2004). The clinical criteria for defining anaphylaxis for this study are listed in Appendix 4. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Appendix 5. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognize and treat anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs, a blood sample will be drawn from the subject as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge for analysis of serum tryptase.

4.5.6 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance.

Subjects will be prompted to take their required dose of ICS/LABA through a trigger in the ePRO. Subjects will also record the dose of ICS/LABA taken in the ePRO. The investigator will assess compliance with background asthma controller medications; subjects will be requested to return used inhalers to study sites to facilitate this assessment. If a subject is judged to be persistently noncompliant with background asthma controller medications, it may be appropriate to withdraw the subject from the study. All subjects should be reminded of the importance of compliance at each study visit.

4.6 Concomitant Medications

4.6.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" as listed in Section 4.6.2.

In addition to the background asthma and rescue medications described in Section 4.5.2.1 and Section 4.5.2.2 respectively, the following concomitant medications related to asthma/allergy treatment are permitted from screening (Week -5) through Week 75:

- Mucolytics and expectorants not containing bronchodilators.
- Maintenance regimen of allergen-specific immunotherapy is allowed but should not be administered within 5 days of investigational product. Subjects should have commenced the regimen for at least 2 months prior to Visit 1 and should remain on a maintenance regimen throughout the study.
- Topical, nasal, and/or ocular formulations of corticosteroids or cromones.
- Topical or oral antihistamines.
- Oral prednisolone up to a maximum of 20 mg daily, or equivalent OCS, for the treatment of chronic asthma.
- Inactivated vaccines.

4.6.2 Excluded Concomitant Medications

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary and are not permitted during the study. The sponsor must be notified if a subject receives any of these during the study

- Immunosuppressive medication (eg, methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid).
- Oral corticosteroid burst or short-acting systemic corticosteroid for reasons other than acute asthma exacerbation.
- Tiotropium bromide.
- Investigational agents.

- Marketed biologics including omalizumab.
- Immunoglobulin or blood products.
- Use of any oral or ophthalmic β-adrenergic antagonist eg, propranolol.
- Subjects are not to begin allergen specific immunotherapy from 2 months before Visit 1.
- Live or attenuated vaccines.

See also Table 5.2.10.3-1 for prohibited medication prior to spirometry assessment.

4.7 Subject Completion

An individual subject will be considered to have completed the study if the subject was followed up through the end of the study, regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.2.3).

4.8 End of the Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study. All materials or supplies provided by the sponsor will be returned to the sponsor or designee upon study completion, as directed by the site monitor. The investigator will notify the IRB/IEC when the study has been completed.

5 Study Procedures

5.1 Schedule of Study Procedures

All subjects who are assigned an SID number and receive any investigational product will be followed according to the protocol regardless of the number of doses received, unless consent is withdrawn. The investigator must notify the sponsor or designee of deviations from protocol visits or evaluations and these evaluations, if applicable, must be rescheduled or performed at the nearest possible time to the original schedule. Protocol deviations will be recorded on the source document with an explanation for the deviation. The investigator must

comply with the applicable requirements related to the reporting of protocol deviations to the IRB/IEC.

Subjects will be instructed to call study personnel to report any abnormalities during the intervals between study visits and to come to the study site if medical evaluation is needed and the urgency of the situation permits. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the investigator and made available to the sponsor or designee during monitoring visits.

A schedule of study procedures is presented in Table 5.1-1 for screening/run-in procedures, Table 5.1-2 for assessments to be performed during the treatment period, and Table 5.1-3 for the follow-up assessment, followed by a description of each visit. A description of the study procedures is included in Section 5.2.

Table 5.1-1 Schedule of Study Procedures for Screening/Run-in Period

Study Week	Week -5	Week -4	Week -2
Study Period	**Screening**	**Run-in**	**Run-in**
Visit	**1**	**2**	**3**
Written informed consent/Assignment of SID	X		
Written informed consent for DNA analysis (if applicable)	X		
Verify eligibility criteria	X	X	
Perform ACQ-6 at site	X		
Medical and asthma history	X		
Concomitant medications	X	X	X
Assessment of AEs and SAEs	X	X	X
Assessment of asthma exacerbations		X	X
Review Personalized Asthma Action Plan	X	X	X
Weight and height	X		
Physical examination	X		
Vital signs	X	X	X
Dispense fluticasone/salmeterol		X	
Review adherence to fluticasone/salmeterol			X
Provide subject's home PFM and ePRO		X	
Check compliance with PFM and ePRO			X
ECG	X		
Chest x-ray (if required)	X		
Serum βHCG (females only)	X		
Urine βHCG (females only)			X
Hepatitis B, C, and HIV testing	X		
Serum for biomarker analysis			X
Whole blood for RNA transcript profiling			X
Total IgE			X
FEIA IgE			X
Serum Chemistry/Hematology/Urinalysis	X		
TB test (if applicable)	X		
Spirometry pre- and post-bronchodilator	X	X	X

Table 5.1-1 Schedule of Study Procedures for Screening/Run-in Period

ACQ-6 = asthma control questionnaire 6-item version; AE = adverse event; βHCG = beta human chorionic gonadotrophin; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ePRO = electronic patient reported outcomes; FEIA = fluorescence enzyme immunoassay; HIV = human immunodeficiency virus; IgE = immunoglobulin E; PFM = peak flow meter; RNA = ribonucleic acid; SAE = serious adverse event; SID = subject identification number; TB = tuberculosis.

Table 5.1-2 Schedule of Study Procedures During the Treatment Period

Procedure	Treatment Period																									
Study Week	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**	**25**	**27**	**29**	**31**	**33**	**35**	**37**	**39**	**41**	**43**	**45**	**47**	**49**	**51**
Visit Number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
Verify randomization criteria and randomize	X																									
Weight	X												X													
Physical examination	X		X				X						X						X						X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of injection sites	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs and SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review adherence to fluticasone/salmeterol and dispense	X		X		X		X		X		X		X		X		X		X		X		X		X	
Review Personalized Asthma Action Plan	X				X				X				X				X				X				X	
Assessment of asthma exacerbations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence to PROs	X		X		X		X		X		X		X		X		X		X		X		X		X	
EQ-5D at study site	X						X						X								X					
ECG	X												X													

Table 5.1-2 Schedule of Study Procedures During the Treatment Period

Procedure	Treatment Period																									
Study Week	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**	**25**	**27**	**29**	**31**	**33**	**35**	**37**	**39**	**41**	**43**	**45**	**47**	**49**	**51**
Visit Number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
Urine βHCG (females only)	X		X		X		X		X		X		X		X		X		X		X		X		X	
Safety biomarkers	X																									
Serum chemistry	X		X		X		X			X			X			X			X						X	
Hematology	X		X		X		X			X			X			X			X						X	
Urinalysis	X		X		X		X			X			X			X			X						X	
FEIA IgE	X						X						X													
Theophylline concentration	X												X													
Serum for trough tralokinumab concentration	X		X				X			X			X						X						X	
Serum for ADA	X																		X							
Serum for biomarker analysis	X		X				X						X													
Whole blood for RNA transcript profiling	X												X													
Total IgE	X						X						X													
Blood sample for DNA (optional)	X																									
Spirometry (pre- & post- bronchodilator)	X	X	X		X		X		X		X		X				X				X				X	

Table 5.1-2 Schedule of Study Procedures During the Treatment Period

Procedure	Treatment Period																									
Study Week	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**	**25**	**27**	**29**	**31**	**33**	**35**	**37**	**39**	**41**	**43**	**45**	**47**	**49**	**51**
Visit Number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
HRCT scan (optional at selected sites only)	X																									
Investigational product administration (Cohort 1)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Investigational product administration (Cohort 2)	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**		**X**	

ADA = anti-drug antibodies; AE = adverse event; βHCG = beta human chorionic gonadotrophin; DNA = deoxyribonucleic acid; ECG = electrocardiogram; FEIA = fluorescence enzyme immunoassay; HRCT = high-resolution computed tomography; IgE = immunoglobulin E; PRO = Patient Reported Outcome; SAE = serious adverse event; RNA = ribonucleic acid.

Table 5.1-3 Schedule of Study Procedures During the Follow-up Period

Procedure	Follow-up/Withdrawal Visits			
Study Week	**53**	**59**	**67**	**75**
Visit	**30**	**31**	**32**	**33/EOS**
Weight	X			X
Physical examination	X			X
Vital signs	X	X	X	X
Assessment of injection sites	X			
Concomitant medications	X	X	X	X
Assessment of AEs and SAEs	X	X	X	X
Review adherence to fluticasone/salmeterol and dispense.	X	X	X	X
Review Personalized Asthma Action Plan	X	X	X	X
Assessment of asthma exacerbations	X	X	X	X
Adherence to PROs	X	X	X	X
EQ-5D	X			X
ECG	X			X
Urine βHCG	X	X	X	X
Serum chemistry/Hematology/Urinalysis	X			X
Theophylline concentration	X			
Serum for tralokinumab concentration	X	X	X	X
Serum for ADA		X		X
Serum for biomarker analysis	X	X	X	X
Whole blood for RNA transcript profiling	X			X
Total IgE	X			X
FEIA IgE	X			X
Spirometry (pre- and post-bronchodilator)	X	X	X	X
HRCT scan (optional at selected sites only)	X			
Collect subject's home PFM and ePRO				X

ADA = anti-drug antibodies; AE = adverse event; βHCG = beta human chorionic gonadotrophin; ECG = electrocardiogram; EOS = End of Study; ePRO = electronic patient reported outcomes; FEIA = fluorescence enzyme immunoassay; HRCT = High-resolution computed tomography; IgE = immunoglobulin E; PFM = peak flow meter; RNA = ribonucleic acid; SAE = serious adverse event.

5.1.1 Screening/Run-in Period

The screening evaluations may be carried out over more than one visit. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations. However, if evaluations that have been performed for other purposes prior to informed consent are otherwise suitable for use as screening evaluations, those evaluations need not be repeated if the subject consents to allow use.

If the screening assessments are not considered to be representative of the usual status of the subject's health by the investigator, repeat screening assessments to establish eligibility will be permitted on one occasion, at the discretion of the investigator. If eligibility assessments cannot be completed due to equipment failure or in other exceptional circumstances that are unrelated to the status of the subject's health, any resulting request for rescreening should be referred to the medical monitor for approval prior to the repeat of any screening assessments.

In the event that repeat screening assessment(s) are required, one of the following approaches should be taken depending on the circumstances:

1) If the screening assessment(s) required to be repeated can be undertaken within the time window defined in Section 5.1.1 for Visit 1 (eg, a repeat blood test), the existing SID number will be used to identify the subject.
2) If the repeat screening assessment(s) required to be repeated cannot be undertaken within the time window defined in Section 5.1.1 for Visit 1 (eg, subjects who have had/have an asthma exacerbation or a clinically significant infection within 30 days prior to Visit 1 or between Visits 1-4), the subject will be considered to have failed screening. If the subject is rescreened, written informed consent should be obtained, a new SID number allocated to the subject, and all Visit 1 assessments performed.

For inclusion in the genetic research (DNA analysis), subjects must also provide an informed consent for genetic research. If a subject declines to participate in the genetic research, there will be no consequence or loss of benefit to the subject. The subject will not be excluded from other aspects of the study described in the protocol, as long as they consent to participate in the main study.

5.1.1.1 Week -5 (Day -35): Screening (Visit 1)

1) Obtain written informed consent, including consent for DNA analysis where appropriate, and appropriate privacy act document authorization

2) Assign an SID number
3) Verify eligibility criteria
4) Perform ACQ-6 at site
5) Perform medical and asthma history
6) Physical examination
7) Measure height and weight
8) Perform ECG
9) Perform chest-x-ray (anterior/posterior and lateral) if not available from the previous 12 months. (Other appropriate lung imaging methods performed within the 12 months before Visit 1 are acceptable if it is normal for an asthmatic subject and excludes significant alternative respiratory disease eg, a chest CT scan.)
10) Measure vital signs
11) Collect blood for screening samples:
    - Serum chemistry
    - Hematology
    - Hepatitis B, C, and HIV
    - Serum beta human chorionic gonadotrophin (βHCG) pregnancy test for women of childbearing potential only
12) Collect urine for urinalysis
13) Perform TB test, if applicable
14) Spirometry pre- and post-bronchodilator. Calculation of reversibility may be repeated at Visit 2 if the subject fails to meet the reversibility criteria at Visit 1.
15) Review Personalized Asthma Action Plan
16) Assess for AEs and SAEs
17) Record concomitant medications

5.1.1.2 Week -4 (Day -28 plus/minus 3 days): Run-in (Visit 2)

1) Verify eligibility criteria
2) Assessment of asthma exacerbations
3) Review Personalized Asthma Action Plan
4) Measure vital signs
5) Spirometry pre and postbronchodilator.
6) Assess for AEs and SAEs

7) Record concomitant medications
8) Dispense fluticasone/salmeterol
9) Provide home peak flow meter (PFM) and ePRO

5.1.1.3 Week -2 (Day -14 plus/minus 3 days): Run-in (Visit 3)

1) Review adherence to fluticasone/salmeterol
2) Check compliance with PFM and ePRO
3) Assessment of asthma exacerbations
4) Review Personalized Asthma Action Plan
5) Collect urine for pregnancy test for women of childbearing potential only (βHCG)
6) Measure vital signs
7) Collect blood for:
    - Serum for biomarker analysis
    - Whole blood for RNA transcript profiling
    - Total IgE
    - FEIA IgE
8) Spirometry pre and postbronchodilator
9) Assess for AEs and SAEs
10) Record concomitant medications

5.1.2 Treatment Period

Each visit during the treatment period may be scheduled within a window of 3 days before or 3 days after the given study day for a visit and every effort should be made to adhere to the stipulated schedule.

5.1.2.1 Week 1 (Day 1 plus/minus 3 days): First Dose for Cohorts 1 and 2 (Visit 4)

1) Verify randomization criteria and randomize
2) Perform EQ-5D at study site
3) Review adherence to PROs (ASMA diary, ACQ-6, AQLQ, WPAI-asthma, and Healthcare Resource Utilization [HRU])
4) Measure weight

5) Perform a physical examination

6) Perform ECG

7) Perform HRCT scan, optional at selected sites only. The HRCT scan should be performed only after the decision to randomize the subject has been made and the scan may be taken either before or after investigational product administration at this Visit.

8) Collect blood predose for:

- Serum chemistry
- Hematology
- Fluorescent enzyme immunoassay (FEIA) IgE
- Total IgE
- Theophylline concentration (if applicable)
- Serum for trough tralokinumab serum concentration and ADA
- Whole blood for RNA transcript profiling
- Serum for biomarker analysis
- Whole blood for safety biomarkers
- Whole blood for DNA (optional)

9) Collect urine for urinalysis and pregnancy test for women of childbearing potential (βHCG); pregnancy test must be negative to receive investigational product.

10) Assessment of asthma exacerbations

11) Spirometry pre and postbronchodilator

12) Record concomitant medications

13) Assess AEs and SAEs

14) Review adherence to fluticasone/salmeterol and dispense

15) Review Personalized Asthma Action Plan

16) Measure predose vital signs

17) Investigational product administration for Cohorts 1 and 2

18) Measure postdose vital signs taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 2 hours.

19) Assess injection site

5.1.2.2 Week 3 (Day 15 plus/minus 3 days): Second Dose for Cohorts 1 and 2 (Visit 5)

1) Assessment of asthma exacerbations
2) Spirometry (pre and postbronchodilator)
3) Record concomitant medications
4) Assess AEs and SAEs
5) Measure predose vital signs
6) Investigational product administration for Cohorts 1 and 2
7) Measure postdose vital signs taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 2 hours.
8) Assess injection site

5.1.2.3 Week 5 (Day 29 plus/minus 3 days): Third Dose for Cohorts 1 and 2 (Visit 6)

1) Review adherence to PROs (ASMA diary, ACQ-6, AQLQ, WPAI-asthma, and HRU)
2) Assessment of asthma exacerbations
3) Spirometry (pre and postbronchodilator)
4) Perform physical examination
5) Collect blood predose for:
   - Serum chemistry
   - Hematology
   - Serum for trough tralokinumab serum concentration
   - Serum for biomarker analysis
6) Collect urine for urinalysis and urine pregnancy test for women of childbearing potential (βHCG); pregnancy test must be negative to receive investigational product.
7) Record concomitant medications
8) Review adherence to fluticasone/salmeterol and dispense
9) Assess AEs and SAEs
10) Measure predose vital signs
11) Investigational product administration for Cohorts 1 and 2

12) Measure postdose vital signs taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 2 hours.

13) Assess injection site

5.1.2.4 Week 7 (Day 43 plus/minus 3 days): Fourth Dose for Cohorts 1 and 2 (Visit 7)

1) Assessment of asthma exacerbations

2) Record concomitant medications

3) Assess AEs and SAEs

4) Measure predose vital signs

5) Investigational product administration for Cohorts 1 and 2

6) Measure postdose vital signs taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 2 hours.

7) Assess injection site

5.1.2.5 Week 9 (Day 57 plus/minus 3 days): Fifth Dose for Cohorts 1 and 2 (Visit 8)

1) Assessment of asthma exacerbations

2) Spirometry (pre and postbronchodilator)

3) Review adherence to PROs (ASMA diary, ACQ-6, AQLQ, WPAI-asthma, and HRU)

4) Review adherence to fluticasone/salmeterol and dispense

5) Review Personalized Asthma Action Plan

6) Assess AEs and SAEs

7) Record concomitant medications

8) Collect blood for predose samples

- Serum chemistry
- Hematology

9) Collect urine for urinalysis and pregnancy test for women of childbearing potential (urine βHCG); pregnancy test must be negative to receive investigational product.

10) Measure predose vital signs

11) Investigational product administration for Cohorts 1 and 2.

12) Measure postdose vital signs; taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 1 hour.

13) Assess injection site

5.1.2.6 Week 11 (Day 71 plus/minus 3 days): Sixth Dose for Cohorts 1 and 2 (Visit 9)

1) Assessment of asthma exacerbations

2) Assess AEs and SAEs

3) Record concomitant medications

4) Measure predose vital signs

5) Investigational product administration for Cohorts 1 and 2.

6) Measure postdose vital signs taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 1 hour.

7) Assess injection site

5.1.2.7 Week 13 (Day 85 plus/minus 3 days): Seventh Dose for Cohorts 1 and 2 (Visit 10)

1) Perform E5-QD at study site

2) Review adherence to PROs (ASMA diary, ACQ-6, AQLQ, WPAI-asthma, and HRU)

3) Review adherence to fluticasone/salmeterol and dispense

4) Assessment of asthma exacerbations

5) Spirometry (pre and postbronchodilator)

6) Perform physical examination

7) Collect blood predose for samples:

- Serum chemistry
- Hematology
- FEIA IgE
- Serum for trough tralokinumab serum concentration
- Serum biomarker analysis
- Total IgE

8) Collect urine for urinalysis and urine pregnancy test for women of childbearing potential (βHCG); pregnancy test must be negative to receive investigational product.

9) Record concomitant medications

10) Assess AEs and SAEs

11) Measure predose vital signs

12) Investigational product administration for Cohorts 1 and 2

13) Measure postdose vital signs; taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 1 hour.

14) Assess injection site

5.1.2.8 Week 15 (Day 99 plus/minus 3 days): Eighth Dose for Cohort 1 (Visit 11)

Assessments as for Week 11, Visit 9.

Investigational product administration for Cohort 1 only.

5.1.2.9 Week 17 (Day 113 plus/minus 3 days): Ninth Dose for Cohort 1 and Eighth Dose for Cohort 2 (Visit 12)

1) Assessment of asthma exacerbations

2) Spirometry (pre and postbronchodilator)

3) Review adherence to PROs (ASMA diary, ACQ-6, AQLQ, WPAI-asthma, and HRU)

4) Review adherence to fluticasone/salmeterol and dispense

5) Review Personalized Asthma Action Plan

6) Assess AEs and SAEs

7) Record concomitant medications

8) Collect urine for pregnancy test for women of childbearing potential (urine βHCG); pregnancy test must be negative to receive investigational product.

9) Measure predose vital signs

10) Investigational product administration for Cohorts 1 and 2

11) Measure postdose vital signs; taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 1 hour.

12) Assess injection site

5.1.2.10 Week 19 (Day 127 plus/minus 3 days): Tenth Dose for Cohort 1 (Visit 13)

1) Assessment of asthma exacerbations
2) Collect blood predose for samples:
   - Serum chemistry
   - Hematology
   - Serum for trough tralokinumab serum concentration
3) Collect urine for urinalysis
4) Record concomitant medications
5) Assess AEs and SAEs
6) Measure predose vital signs
7) Investigational product administration (Cohort 1 only)
8) Measure postdose vital signs; taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 1 hour.
9) Assess injection site

5.1.2.11 Week 21 (Day 141 plus/minus 3 days): Eleventh Dose for Cohort 1 and Ninth Dose for Cohort 2 (Visit 14)

1) Review adherence to PROs (ASMA diary, ACQ-6, AQLQ, WPAI-asthma, and HRU)
2) Review adherence to fluticasone/salmeterol and dispense
3) Assessment of asthma exacerbations
4) Spirometry (pre and postbronchodilator)
5) Collect urine for pregnancy test for women of childbearing potential (βHCG); pregnancy test must be negative to receive investigational product.
6) Review concomitant medications
7) Assess AEs and SAEs
8) Measure predose vital signs
9) Investigational product administration for Cohorts 1 and 2
10) Measure postdose vital signs; taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 1 hour.
11) Assess injection site

5.1.2.12 Week 23 (Day 155 plus/minus 3 days): Twelfth Dose for Cohort 1 (Visit 15)

Assessments as for Week 11, Visit 9.

Investigational product administration for Cohort 1 only.

5.1.2.13 Week 25 (Day 169 plus/minus 3 days): Thirteenth Dose for Cohort 1 and Tenth Dose for Cohort 2 (Visit 16)

1) Perform EQ-5D at study site
2) Review adherence to PROs (ASMA diary, ACQ-6, AQLQ, WPAI-asthma, and HRU)
3) Measure weight
4) Perform a physical examination
5) Perform ECG
6) Collect blood predose for samples:
   - Serum chemistry
   - Hematology
   - FEIA IgE
   - Total IgE
   - Theophylline concentration (if applicable)
   - Serum for trough tralokinumab serum concentration
   - Whole blood for RNA transcript profiling
   - Serum for biomarker analysis
7) Collect urine for urinalysis and pregnancy test for women of childbearing potential (βHCG); pregnancy test must be negative to receive investigational product.
8) Assessment of asthma exacerbations
9) Spirometry pre and postbronchodilator
10) Record concomitant medications
11) Assess AEs and SAEs
12) Review adherence to fluticasone/salmeterol and dispense
13) Review Personalized Asthma Action Plan
14) Measure predose vital signs
15) Investigational product administration for Cohorts 1 and 2

16) Measure postdose vital signs; taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 1 hour.

17) Assess injection site

5.1.2.14 Week 27 (Day 183 plus/minus 3 days): Fourteenth Dose for Cohort 1 (Visit 17)

Assessments as for Week 11, Visit 9.

Investigational product administration for Cohort 1 only.

5.1.2.15 Week 29 (Day 197 plus/minus 3 days): Fifteenth Dose for Cohort 1 and Eleventh Dose for Cohort 2 (Visit 18)

1) Review adherence to PROs (ASMA diary, ACQ-6, AQLQ, WPAI-asthma, and HRU)

2) Review adherence to fluticasone/salmeterol and dispense

3) Assessment of asthma exacerbations

4) Collect urine for pregnancy test for women of childbearing potential (βHCG); pregnancy test must be negative to receive investigational product.

5) Review concomitant medications

6) Assess AEs and SAEs

7) Measure predose vital signs

8) Investigational product administration for Cohorts 1 and 2

9) Measure postdose vital signs; taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 1 hour.

10) Assess injection site

5.1.2.16 Week 31 (Day 211 plus/minus 3 days): Sixteenth Dose for Cohort 1 (Visit 19)

1) Assessment of asthma exacerbations

2) Collect blood predose for samples:

- Serum chemistry
- Hematology

3) Collect urine for urinalysis

4) Record concomitant medications

5) Assess AEs and SAEs

6) Measure predose vital signs

7) Investigational product administration (Cohort 1 only)

8) Measure postdose vital signs; taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 1 hour.

9) Assess injection site

5.1.2.17 Week 33 (Day 225 plus/minus 3 days): Seventeenth Dose for Cohort 1 and Twelfth Dose for Cohort 2 (Visit 20)

Assessments as for Week 17, Visit 12.

5.1.2.18 Week 35 (Day 239 plus/minus 3 days): Eighteenth Dose for Cohort 1 (Visit 21)

Assessments as for Week 11, Visit 9.

Investigational product administration for Cohort 1 only.

5.1.2.19 Week 37 (Day 253 plus/minus 3 days): Nineteenth Dose for Cohort 1 and Thirteenth Dose for Cohort 2 (Visit 22)

1) Review adherence to PROs (ASMA diary, ACQ-6, AQLQ, WPAI-asthma, and HRU)

2) Review adherence to fluticasone/salmeterol and dispense

3) Assessment of asthma exacerbations

4) Perform physical examination

5) Collect blood predose for samples:

- Serum chemistry
- Hematology
- Serum for trough tralokinumab serum concentration and ADA

6) Collect urine for urinalysis and pregnancy test for women of childbearing potential (βHCG); pregnancy test must be negative to receive investigational product.

7) Review concomitant medication

8) Assess AEs and SAEs

9) Measure predose vital signs

10) Investigational product administration for Cohorts 1 and 2

11) Measure postdose vital signs; taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 1 hour.

12) Assess injection site

5.1.2.20 Week 39 (Day 267 plus/minus 3 days): Twentieth Dose for Cohort 1 (Visit 23)

Assessments as for Week 11, Visit 9.

Investigational product administration for Cohort 1 only.

5.1.2.21 Week 41 (Day 281 plus/minus 3 days): Twenty-first Dose for Cohort 1 and Fourteenth Dose for Cohort 2 (Visit 24)

1) Perform EQ-5D at study site

2) Review adherence to PROs (ASMA diary, ACQ-6, AQLQ, WPAI-asthma, and HRU)

3) Assessment of asthma exacerbations

4) Spirometry (pre and postbronchodilator)

5) Review adherence to fluticasone/salmeterol and dispense

6) Review Personalized Asthma Action Plan

7) Assess AEs and SAEs

8) Record concomitant medications

9) Collect urine for pregnancy test for women of childbearing potential (urine βHCG); pregnancy test must be negative to receive investigational product.

10) Measure predose vital signs

11) Investigational product administration

12) Measure postdose vital signs; taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 1 hour.

13) Assess injection site

5.1.2.22 Week 43 (Day 295 plus/minus 3 days): Twenty-second Dose for Cohort 1 (Visit 25)

Assessments as for Week 11, Visit 9.

Investigational product administration for Cohort 1 only.

5.1.2.23 Week 45 (Day 309 plus/minus 3 days): Twenty-third Dose for Cohort 1 and Fifteenth Dose for Cohort 2 (Visit 26)

Assessments as for Week 29, Visit 18.

5.1.2.24 Week 47 (Day 323 plus/minus 3 days): Twenty-forth Dose for Cohort 1 (Visit 27)

Assessments as for Week 11, Visit 9.

Investigational product administration for Cohort 1 only.

5.1.2.25 Week 49 (Day 337 plus/minus 3 days): Twenty-fifth Dose for Cohort 1 and Sixteenth Dose for Cohort 2 (Visit 28)

1) Review adherence to PROs (ASMA diary, ACQ-6, AQLQ, WPAI-asthma, and HRU)
2) Assessment of asthma exacerbations
3) Spirometry (pre and postbronchodilator)
4) Perform physical examination
5) Collect blood predose for samples:
   - Serum chemistry
   - Hematology
   - Serum for trough tralokinumab serum concentration
6) Collect urine for urinalysis and pregnancy test for women of childbearing potential (βHCG); pregnancy test must be negative to receive investigational product.
7) Review adherence to fluticasone/salmeterol and dispense
8) Review Personalized Asthma Action Plan
9) Record concomitant medication
10) Assess AEs and SAEs
11) Measure predose vital signs
12) Investigational product administration for Cohorts 1 and 2
13) Measure postdose vital signs; taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable for a minimum of 1 hour.
14) Assess injection site

5.1.2.26 Week 51 (Day 351 plus/minus 3 days): Twenty-sixth Dose for Cohort 1 (Visit 29)

Assessments as for Week 11, Visit 9.

Investigational product administration for Cohort 1 only.

5.1.2.27 Unscheduled Dosing Visit

In exceptional circumstances, when it has not been possible for a subject to attend a scheduled visit for administration of investigational product, an unscheduled dosing visit may be required to ensure that a prolonged period between administrations of investigational product does not occur (this is especially relevant for Cohort 2). An unscheduled dosing visit must not occur within 7 days of a subsequent scheduled visit at which investigational product is to be administered.

1) Assessment of asthma exacerbations
2) Record concomitant medications
3) Assess AEs and SAEs
4) Measure predose vital signs
5) Investigational product administration
6) Measure postdose vital signs
7) Assess injection site

5.1.3 Follow-up/Withdrawal Visits

5.1.3.1 Week 53 (Day 365 plus/minus 7 days): Follow-up (Visit 30)

1) Perform E5-QD at study site
2) Review adherence to PROs (ASMA diary, ACQ-6, AQLQ, WPAI-asthma, and HRU)
3) Assessment of asthma exacerbations
4) Spirometry (pre and postbronchodilator)
5) Measure weight
6) Perform a physical examination
7) ECG
8) Perform HRCT scan (optional at selected sites only and only those subjects who had a visually acceptable HRCT scan at Visit 4)

9) Review adherence to fluticasone/salmeterol and dispense
10) Review Personalized Asthma Action Plan
11) Collect blood for:
    - Serum chemistry
    - Hematology
    - Theophylline concentration (if applicable)
    - Serum for tralokinumab concentration
    - Serum for biomarker analysis
    - Whole blood for RNA transcript profiling
    - Total IgE
    - FEIA IgE
12) Collect urine for urinalysis and pregnancy test for women of childbearing potential (urine βHCG)
13) Measure vital signs
14) Assess injection sites
15) Record concomitant medications
16) Assess AEs and SAEs

5.1.3.2 Week 59 (Day 407 plus/minus 7 days): Follow-up (Visit 31)

1) Review adherence to PROs (ASMA diary, ACQ-6, and AQLQ)
2) Assessment of asthma exacerbations
3) Spirometry (pre and postbronchodilator)
4) Review adherence to fluticasone/salmeterol and dispense
5) Review Personalized Asthma Action Plan
6) Collect blood for:
    - Serum for tralokinumab concentration and ADA
    - Serum for biomarker analysis
7) Collect urine for pregnancy test for women of childbearing potential (urine βHCG)
8) Measure vital signs
9) Record concomitant medications
10) Assess AEs and SAEs

5.1.3.3 Week 67 (Day 463 plus/minus 7 days): Follow-up (Visit 32)

1) Review adherence to PROs (ASMA diary, ACQ-6, and AQLQ)
2) Assessment of asthma exacerbations
3) Spirometry (pre and postbronchodilator)
4) Review adherence to fluticasone/salmeterol and dispense
5) Review Personalized Asthma Action Plan
6) Collect blood for:
   - Serum for tralokinumab concentration
   - Serum for biomarker analysis
7) Collect urine for pregnancy test for women of childbearing potential (urine βHCG)
8) Measure vital signs
9) Record concomitant medications
10) Assess AEs and SAEs

5.1.3.4 Week 75 (Day 519 plus/minus 7 days): Follow-up (Visit 33)/End of Study Visit

1) Perform E5-QD at study site
2) Review adherence to PROs (ASMA diary, ACQ-6, and AQLQ)
3) Assessment of asthma exacerbations
4) Spirometry (pre and postbronchodilator)
5) Measure weight
6) Perform a physical examination
7) ECG
8) Review adherence to fluticasone/salmeterol
9) Review Personalized Asthma Action Plan
10) Collect blood for:
   - Serum chemistry
   - Hematology
   - Serum for tralokinumab concentration and ADA
   - Serum for biomarker analysis
   - Whole blood for RNA transcript profiling

- Total IgE
- FEIA IgE

11) Collect urine for urinalysis and pregnancy test for women of childbearing potential (urine βHCG)

12) Measure vital signs

13) Record concomitant medications

14) Assess AEs and SAEs

15) Collect subject's home PFM and ePRO

5.2 Description of Study Procedures

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

5.2.1 Medical History and Asthma History

Complete medical history will include history and current medical conditions, past or present cardiovascular disorders, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, psychiatric, genitourinary, drug and surgical history, or any other diseases or disorders.

The asthma history questionnaire, also completed as part of the screening evaluations, includes questions related to the subject's asthma history, duration of asthma, asthma medications, and number of exacerbations/hospitalizations and treatments in the previous 13 months.

5.2.2 Physical Examination, Electrocardiogram, Weight, Height, and Vital Signs

Physical examinations will be performed by a physician or qualified designee and will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, abdominal system, and nervous system. Medically significant changes from the screening physical examination will be considered AEs and recorded as such on the collection instrument provided.

Height and weight will be measured as indicated in Table 5.1-1, Table 5.1-2, and Table 5.1-3.

5.2.2.1 Vital Signs

Vital signs (blood pressure, temperature, pulse rate, and respiration rate) will be obtained before investigational product administration on all treatment days. After investigational product administration, subjects will be monitored for immediate drug reactions; vital signs will be taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter. For the first 4 doses of investigational product, subjects will remain at site for a minimum of 2 hours or until stable, whichever is later. For the fifth and subsequent doses of investigational product, subjects will remain at site a minimum of 1 hour or until stable, whichever is later. Discharge from site will be determined by the investigator.

Subjects in Cohort 2 require vital signs to be measured only once during the visits at which they are not receiving investigational product.

Vital signs (blood pressure, temperature, pulse rate, and respiration rate) will be obtained at each visit after the subject has been resting for at least 5 minutes. Subjects should be seated and pulse rate will be measured before blood pressure.

5.2.2.2 Electrocardiogram

Computerized 12-lead ECG recordings will be obtained after the subject has been supine for at least 10 minutes. Each lead will be recorded for at least 3-5 beats at a speed of 25 mm/sec paper speed and 10 mm/mV amplitude. Heart rate, PR, QRS, QT and QTc intervals (msec) will be recorded from the 12-lead ECG. The principal investigator or a designated subinvestigator will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. The ECG will also be transmitted to a central reader to quantitatively assess PR, QRS, QT, and QTc intervals.

5.2.3 Chest X-ray for Screening

If required, a chest x-ray will be completed during the screening period. The chest x-ray may be substituted with documentation of a previous chest x-ray or other appropriate lung imaging method eg, chest CT scan performed within the previous 12 months that meets inclusion criterion 10 (Section 4.2.1).

5.2.4 Clinical Laboratory Tests

Clinical laboratory safety tests including serum pregnancy tests will be performed in a central clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal laboratory results that are considered clinically relevant by the investigator should be repeated as soon as possible (preferably within 24-48 hours). These repeat tests may either be performed by the central clinical laboratory or by a laboratory local to the site as clinically indicated. If the urine dipstick test is abnormal, with a result greater than negative or trace, then a urine microscopy and culture will be performed.

The following clinical laboratory tests will be performed (see Table 5.1-1, Table 5.1-2, and Table 5.1-3 for the schedule of tests):

Serum Chemistry

- Calcium
- Chloride
- Potassium
- Sodium
- Bicarbonate
- Aspartate transaminase (AST)
- Alanine transaminase (ALT)
- Gamma glutamyl transferase (GGT)
- Uric acid
- Creatinine
- Total bilirubin
- Glucose
- Alkaline phosphatase (ALP)
- Blood urea nitrogen (BUN)

Hematology

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hematocrit
- Hemoglobin
- Platelet count
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)

Urinalysis

- Nitrites (dipstick)
- Protein (dipstick)
- Glucose (dipstick)
- Ketones (dipstick)
- Blood (dipstick)
- Bilirubin (dipstick)
- Urine microscopy and urine casts (as required)
- Urine culture (as required)

Pregnancy Test (females of childbearing potential only)

- Urine human chorionic gonadotropin (hCG)
- Serum beta-hCG (at screening only)

Other Safety Tests

- Hepatitis B surface antigen, hepatitis C antibody (screening only)
- HIV-1 and HIV-2 antibody (screening only)
- Theophylline
- Safety biomarkers
- TB test if applicable, as per local standard of care guidelines

Other Tests

- Total IgE
- Serum IgE FEIA to common aeroallergens
- Serum biomarkers and RNA transcript profiling
- Serum tryptase

5.2.5 Measurement of Theophylline Levels

Theophylline has a narrow therapeutic index, several potential drug interactions and altered clearance with changes in physiology, periodic monitoring of serum levels are required with chronic use (see Appendix 6). For subjects entering the study taking theophylline, serum levels will be obtained at Weeks 1 (Day 1), 25, and 53. In most individuals a peak steady-state plasma theophylline concentration of between 10-20 mg/L is adequate for satisfactory bronchodilation, while the frequency of adverse effects increases at concentrations above 20 mg/L. If subjects require new, chronic, non-asthma medications that are known to interact with theophylline during the course of the study, the investigator should adjust the theophylline dose accordingly and obtain a new steady-state theophylline serum level. Lastly, if the subject develops an AE or SAE requiring an emergency room visit or hospitalization, it is recommended that a theophylline level should be obtained as part of the medical evaluation.

5.2.6 Assessment of Injection Sites

The site of injection will be assessed at every visit from Week 1 through Week 53. Injection site reactions will be recorded as AEs according to the criteria described in Section 6.1.1.

5.2.7 Pharmacokinetic Evaluation and Methods

For PK analyses, it is important that the time of the first SC injection is recorded for each subject. Serum will be collected predose according to the schedule of study procedures to

measure trough tralokinumab levels. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to sites.

5.2.8 Immunogenicity Evaluation and Methods

Serum samples to measure the presence of ADA will be collected according to the schedule of study procedures. Instructions for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to the sites.

5.2.9 Biomarker Evaluation and Methods

5.2.9.1 Serum Biomarkers

Serum samples will be collected according to the schedule of study procedures to assess serum biomarkers to include analysis of pro-inflammatory mediators.

5.2.9.2 RNA Transcript Profiling

PAXgene whole blood samples will be collected as indicated in the schedule of study procedures for whole genome RNA transcript analysis. The purpose of these analyses will be to retrospectively evaluate whole blood transcript biomarkers predictive of subject response as well as to potentially identify additional pharmacodynamic biomarkers.

5.2.9.3 DNA Sample (Optional)

To investigate characteristics associated with subjects' clinical response and safety, one blood sample (8.5 mL) may be collected on Week 1 (Day 1) and frozen at –70°C for DNA sample preparation. The sample will be frozen and stored until used in exploratory analyses. The collection of blood for DNA analysis is optional. The completion of a separate ICF is requested but not required for participation in the study. Subjects who do not wish to have the DNA test done will still be eligible for the study. Subjects who elect to have the DNA test done may, at any time before the end of the study, request that the blood collected for DNA analysis be destroyed. All specimen and subject identifiers must be removed from the DNA blood samples such that under no circumstances can the DNA blood samples be linked back to a specific subject.

5.2.9.4 Safety Biomarkers

Serum samples will be collected at Week 1 (Day 1) for baseline assessment of safety biomarkers. If an anaphylactic reaction (see Appendix 4) occurs during or within a 24-hour period after administration of investigational product, whole blood for assessment of safety biomarkers will be collected as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge.

5.2.10 Disease Evaluation and Methods

5.2.10.1 Personalized Asthma Action Plan

A Personalized Asthma Action Plan will be created by the investigator to assist subjects in making appropriate changes in their asthma medical treatment in response to changes in their asthma control. These guidelines will be a written, predetermined document created by the investigator and given to subjects at Visit 1 (Week -5). The Personalized Asthma Action Plan will be reviewed as indicated in the schedule of study procedures. An example of a Personalized Asthma Action Plan can be found in Appendix 7.

5.2.10.2 Asthma Exacerbations

For the purpose of this study, an asthma exacerbation occurring after Visit 1 is defined as a progressive increase of asthma symptoms (cough, wheeze, chest tightness, and/or shortness of breath) that does not resolve after the initiation of rescue medications and remains troublesome for the subject resulting in either 1) use of systemic corticosteroids (tablets, suspension or injection) or increase of a stable systemic maintenance dose for a duration of at least 3 consecutive days as prescribed or administered by the investigator or healthcare provider; or 2) subject initiation of systemic corticosteroids for a duration of at least 3 consecutive days as outlined in the Asthma Action Plan provided to the subject by the investigator on Day 1 (see Appendix 7).

An asthma exacerbation event will be considered resolved 7 days after the last dose of OCS is administered (10 days after administration of an injectable corticosteroid). Courses of corticosteroids initiated after this time period would be considered a separate new asthma exacerbation.

Asthma exacerbation severity will be classified as follows:

- Moderate: Worsening symptoms requiring systemic corticosteroids for at least 3 consecutive days.
- Severe: Worsening symptoms requiring systemic corticosteroids and requiring urgent care evaluation and/or hospital admission.

5.2.10.3 Spirometry

Spirometry will be performed by the investigator or qualified designee on equipment provided by a central vendor according to ATS/European Respiratory Society (ERS) guidelines (Miller et al, 2005). The following values will be captured: pre- and post-bronchodilator FEV_1, FEV_6, FVC, and IC.

Spirometry testing must be performed in the morning between 6:00 and 11:00 AM according to the schedule of study procedures. On treatment days, spirometry testing will be performed before administration of investigational product.

All morning spirometry testing must be completed between 6.00 and 11.00 AM and within ± 1 hour of the time the screening spirometry was completed. For example, if the screening spirometry is at 8:00 AM, then all spirometry testing at subsequent visits need to be completed between 7:00 and 9:00 AM.

Subjects will be required to refrain from strenuous exercise for 30 minutes prior to spirometry testing and to withhold the following medications or food prior to spirometry testing (Table 5.2.10.3-1). If a subject has taken these medications prior to a pre-arranged site visit, they should contact the site to reschedule their assessment visit.

Table 5.2.10.3-1 Prohibited Medication or Food and Minimum Time Intervals Prior to Spirometry Testing

Concomitant Medication or Food	Minimum Time Interval from Last Medication Dose or Food to Spirometry Testing
Inhaled bronchodilators	
SABAs (albuterol/salbutamol, levalbuterol, etc.)	6 hours
LABAs (salmeterol, formoterol)	12 hours
Ipratropium bromide	8 hours
Cromolyn	8 hours
Nedocromil	24 hours
Oral bronchodilators	
eg, Theophylline	24 hours
Other medications	
Leukotriene modifiers	24 hours
Foods	
All caffeinated beverages (eg, coffee, tea, cola drinks, Mellow Yellow, Mountain Dew), chocolate (caffeinated foods), alcohol	12 hours

LABA = long-acting β2 agonist; SABA = short-acting β2 agonist

Subjects should be sitting during spirometry testing; however, if the subject is unable to sit, then standing is acceptable. Spirometry testing should be completed in the same manner (ie, sitting or standing) at every study visit. Nose clips will be used for clinic spirometry.

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each clinic spirometry session and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded. The best efforts will be based on the highest FEV_1. The maximum FEV_1 of the 2 best efforts will be used for the analysis. The absolute measurement (for FEV_1 and FVC), and the percentage of predicted normal value will be recorded using appropriate reference values. The highest FVC will also be reported regardless of the effort in which it occurred (even if the effort did not result in the highest FEV_1. Inspiratory capacity will be recorded using a slow spirometry manoeuvre; the best effort following a minimum of 3 IC measurements will be recorded.

Equipment, training, and a procedures manual will be provided to the site by a qualified vendor.

5.2.10.4 Pre- and Post-bronchodilator FEV1 and FVC Measurements Including Reversibility Calculations

Pre- and post-bronchodilator FEV_1 and FVC will be performed at each spirometry assessment. The reversibility assessment will be performed as follows:

1) Prebronchodilator FEV_1 measurement will be assessed as described above (Section 5.2.10.3).
2) After a gentle and incomplete expiration, a dose of 100 µg of salbutamol (or equivalent short acting bronchodilator) will be inhaled in one breath to total lung capacity from a spacer device.
3) Breath is then held for 5–10 seconds before the subject exhales. Four separate doses of 100 µg of salbutamol are delivered at 30 second intervals.
4) Wait 15-30 minutes (30 minutes if a short-acting anticholinergic agent is used).
5) Postbronchodilator FEV_1 measurement will be assessed and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded. The maximum FEV_1 of the 2 best efforts will be used for the analysis.

Each subject should use the same dose and type of short acting bronchodilator throughout the study. Total doses of less than 400 µg of salbutamol or equivalent may be used for the reversibility assessment at the discretion of the investigator if there are concerns about side effects (eg, heart rate or tremor).

Reversibility is calculated as follows:

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

5.2.10.5 Home Peak Flow Testing

Home peak flow testing for FEV_1 and PEF will be performed twice daily, in the morning upon awakening and in the evening prior to bedtime from Visit 2 through the Week 75 visit using a PFM. Testing should be made while standing and should be performed before intake of maintenance treatment upon rising in the morning and at bedtime in the evening. Sites will check subject adherence from Visit 3 through the Week 75 visit. Subjects should perform peak flow testing while sitting or standing, but in the same position at every testing. Peak

flow meters for home and instructions for data recording will be provided to each enrolled subject at Visit 2.

5.2.10.6 Computed Tomography

Asthma is characterized by chronic inflammation of the airways and pathologic structural changes such as subepithelial fibrosis, increased reticular basement membrane thickness, an increase in mucus-producing goblet cells, increased mucus production from submucosal glands, angiogenesis, and an increase in smooth muscle mass. These changes are collectively known as airway remodeling. Prevention or reversal of airway remodeling may be important in preventing the irreversible component of impaired lung function seen in asthma.

High-resolution computerized tomography is a well-established technique (ACR Practice Guidelines, 2010) that allows detailed visualization of airways and parenchyma and provides an opportunity to investigate the site, magnitude, and distribution of airway abnormalities. As described in the ACR guidelines, HRCT can be performed using both sequential (axial) or spiral (helical) scanning modes. High-resolution computerized tomography scans obtained using spiral scanning have been used to measure airway thickening in patients with asthma and changes in airway dimensions have been shown in asthmatics treated with anti-inflammatory agents such as beclomethasone (Niimi et al, 2004), budesonde, and formoterol (Capraz et al, 2007; Wang et al 2011), and mepolizumab (Halder et al, 2009).

In this study HRCT with spiral scanning will be used to determine the effects of tralokinumab administration on airway wall structural change, an important component of airway remodeling. Parameters including airway wall thickness, lumen diameter, and airway diameter will be measured.

This substudy has been designed with reference to the EU guidance (Directorate-General Environment, Nuclear Safety and Civil Protection, 1998). The potential benefits of the study are expected to be Category IIB as described in the guidance document aimed directly at the diagnosis, cure, or prevention of disease. The use of HRCT involves ionizing radiation that increases the risk of radiogenic tumors in patients and since receipt of 2 HRCT scans in this study may not offer direct individual benefit to the subject, a dose constraint has been applied based on the ALARA (As Low As Reasonably Achievable) principle. The total radiation dose resulting from 2 scans (considering the variation between scanners at different sites) is estimated to be in the range of 2-5 mSv (HRCT radiation dose was < 1 mSv for 1.5 mm thick slices with a 10 mm gap; Van der Bruggen-Bogaarts et al, 1995). This dose is within the

accepted radiation dose range for biological research (1-10 mSv; Directorate-General Environment, Nuclear Safety and Civil Protection, 1998).

Selected sites will participate in this HRCT substudy and participation will be optional for subjects at these sites. An adequate number of sites will be identified in order to target recruitment of approximately 40 subjects from each of the 2 cohorts into the HRCT substudy; this target number of subjects is derived from examples in the literature where changes in airway measures have been demonstrated in subjects with asthma following treatment intervention as described above. Participating sites will be provided with a separate manual containing all necessary instructions for HRCT assessments. A wide range of CT scanners are expected to be used across different sites and each site will be qualified to ensure that the scanner hardware and performance meet the quality standards required for longitudinal CT studies. In addition phantom scans and calibration data will be used to ensure stable performance of the scanners at each site during the study follow-up period.

Selected sites will be provided with a separate imaging manual containing all necessary instructions for HRCT assessment. Information for the potential risks of radiation will be provided to the subjects during the informed consent process.

Each subject will receive 2 inspiratory scans as described in the Imaging Protocol, one at each of Visits 4 and 30; (Day 1 and Week 53, respectively). The first scan will occur after randomization on Visit 4 (Day 1) and can be done before or after investigational product administration as convenient. The scan must be visually acceptable with no artifacts related to motion, streak, or metal. The second assessment will be performed at Visit 30, (Week 53) but only for subjects with readable Day 1 scan.

Images will be transferred to a central reader at a specialist Contract Research Organisation for analysis as described in the Imaging Protocol.

5.2.11 Patient Reported Outcomes

5.2.11.1 Asthma Control Questionnaire

The ACQ is a patient-reported questionnaire assessing asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing) and daily rescue bronchodilator use and FEV_1 (Juniper, O'Byrne et al, 1999).

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 β2 agonist use) omitting the FEV_1 measurement from the original ACQ score. The ACQ-6 will be completed at site during Visit 1 (Week -5). Subjects will be provided with the ePRO device at Visit 2 and will complete the ACQ-6 at home weekly between Visits 2 and 4, and every 4 weeks thereafter through Visit 33 (Week 75). Sites will check subject adherence with the ACQ as indicated in the schedule of study procedures through Visit 33 (Week 75). Subjects are asked to recall how their asthma has been during the previous week by responding to one bronchodilator use question and 5 symptom questions.

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and < 1.5 indicate partly-controlled asthma, and a score ≥ 1.5 indicates uncontrolled asthma (Juniper et al, 2006). Individual changes of at least 0.5 are considered to be clinically meaningful (Juniper et al, 2005).

5.2.11.2 Asthma Quality of Life Questionnaire (Standardised Version)

The AQLQ(S) is a 32-item questionnaire that measures the HRQoL experienced by asthma patients (Juniper, Buist et al, 1999) and will be completed at the Week 1 visit, and then every 4 weeks at home through the Week 75 visit using an ePRO device. Sites will check subject adherence at select visits through the Week 75 visit.

The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli). Subjects are asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The 4 individual domain scores (symptoms, activity limitations, emotional function, and environmental stimuli) are the means of the responses to the questions in each of the domains. Individual improvement in both the overall score and individual domain scores of 0.5 has been identified as a minimally important change, with score changes of > 1.5 identified as large meaningful changes (Juniper et al, 1994).

5.2.11.3 Assessing Symptoms of Moderate-to-severe Asthma Diary

The ASMA Diary is a 13-item questionnaire developed by MedImmune and UBC. The ASMA Diary will be assessed each morning from Visit 2 (Week -4) through the Week 75

visit using an ePRO device. Sites will check subject adherence as part of the inclusion criteria (at least 8 (any 8) of the last 10 days of the screening/run-in period) and at as indicated in the schedule of assessments. Subjects are asked to recall their experience with daytime and nighttime symptom frequency and severity, activity avoidance and limitation, asthma-related anxiety and fatigue as well as rescue medication use.

5.2.11.4 ASMA Diary Anchor Questions

Seven questions about the subjects' symptoms and overall disease will be assessed at Weeks 1, 13, 25, 41, 53, and 75 using an ePRO device. These questions will be used to assist with the creation of responder definitions for the new ASMA Diary developed by MedImmune and UBC.

5.2.11.5 Work Productivity and Activity Impairment Questionnaire - Asthma (WPAI-Asthma)

The WPAI-Asthma will be used to measure self-reported productivity loss and will be completed every 4 weeks at home from Week 1 through the Week 53 visit using an ePRO device. Sites will check subject adherence at as indicated in the schedule of assessments. The WPAI-Asthma consists of questions about absence from work due to asthma problems, hours actually worked, the reduction in productivity at work and about the reduction in productivity while performing regular activities. The questionnaire relates to the previous 7 days.

5.2.11.6 EQ-5D

The EQ-5D will be completed at the site at Weeks 1 (Day 1), 13, 25, 41, 53, and 75. The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (EuroQol Group, 1990). Each dimension has 3 response options (no problem, some or moderate problems, and unable or extreme problems) that reflect increasing levels of difficulty. The respondent is asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analog scale, where the subjects are asked to rate their current health on a scale of 0-100, with 0 being the worst imaginable health state.

5.2.12 Healthcare Resource Utilization

Asthma-related HRU will be assessed weekly at home from Week 1 (Day 1) through the Week 53 visit using an ePRO device. Sites will check subject adherence at as indicated in the schedule of assessments.

5.2.13 Estimate of Volume of Blood to Be Collected

Table 5.2.13-1 An Estimate of Blood Volume to be Taken

Visit Number	Week Number	Volume of Blood (mL)
1	-5	14.0
2	-4	0.0
3	-2	14.5
4	1	47.5
5	3	0.0
6	5	21.5
7	7	0.0
8	9	14.0
9	11	0.0
10	13	25.5
11	15	0.0
12	17	0.0
13	19	17.5
14	21	0.0
15	23	0.0
16	25	30.5
17	27	0.0
18	29	0.0
19	31	14.0
20	33	0.0
21	35	0.0
22	37	22.5
23	39	0.0
24	41	0.0
25	43	0.0
26	45	0.0
27	47	0.0
28	49	17.5
29	51	0.0
30	53	32.0

Table 5.2.13-1 An Estimate of Blood Volume to be Taken

Visit Number	Week Number	Volume of Blood (mL)
31	59	12.5
32	67	7.5
33	75	35.0

6 Assessment of Safety

6.1 Safety Parameters

6.1.1 Adverse Events

The ICH Guideline for Good Clinical Practice E6(R1) defines an AE as:

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including electrocardiogram [ECG] finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical

event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

Asthma exacerbations reported by study subjects that fulfill the protocol definition (Section 5.2.10.2) should be recorded as AEs or SAEs as appropriate. For asthma exacerbations, that do not fulfill the protocol definition (eg, worsening of asthma symptoms not resulting in the administration of a corticosteroid burst), the investigator should decide whether or not to report these as adverse events on the case report form.

6.1.2 Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening

  This term refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that may have led to death.

- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in an outpatient setting.

- Results in persistent or significant disability/incapacity

  The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

  Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

6.2 Assessment of Safety Parameters

6.2.1 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

6.2.2 Assessment of Relationship

6.2.2.1 Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered "not related" to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

6.2.2.2 Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.

Not protocol related: The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

6.3 Recording of Safety Parameters

6.3.1 Recording of Adverse Events and Serious Adverse Events

Adverse events will be recorded on the CRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to MedImmune Patient Safety. See Section 6.1.2 for the definition of SAEs, and Section 6.2.1 and Section 6.2.2 for guidelines for assessment of severity and relationship, respectively. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

6.4 Reporting Requirements for Safety Parameters

6.4.1 Study Reporting Period and Follow-up for Adverse Events

The reporting period for AEs is the period immediately following the time that written informed consent is obtained through the end of subject participation in the study.

New (nonserious) AEs that start after the reporting period has ended will not be collected. All AEs that start during the reporting period will be followed to resolution through the end of subject participation in the study.

6.4.2 Reporting of Serious Adverse Events

6.4.2.1 Study Reporting Period and Follow-up for Serious Adverse Events

The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through the end of subject participation in the study. After submitting an initial SAE report for a subject (to MedImmune Patient Safety), the investigator is required to follow the subject proactively and provide further information on the subject's condition to MedImmune Patient Safety.

At any time after completion of the study, if an investigator or qualified designee becomes aware of an SAE that is suspected by the investigator or qualified designee to be related to investigational product, the event must be reported to MedImmune Patient Safety.

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

6.4.2.2 Notifying the Sponsor of Serious Adverse Events

Within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must complete the SAE Report Form and fax it to MedImmune Patient Safety.

MedImmune contact information:

Patient Safety
MedImmune
[redacted]

The sponsor is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH Guidelines and/or local regulatory requirements (see Section 6.4.2.3). The sponsor may be required to report certain SAEs to regulatory authorities within

7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the sponsor as soon as it becomes available.

Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying MedImmune Patient Safety of an SAE. When additional information becomes available, investigators should submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Patient Safety within 24 hours of learning of the new information.

6.4.2.3 Safety Reporting to Investigators, Institutional Review Boards or Independent Ethics Committees, and Regulatory Authorities

The sponsor is responsible for reporting all applicable SAEs to regulatory authorities, investigators, and IRBs/IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational product or that would be sufficient to consider changes in the administration of the investigational product or in the overall conduct of the study.

For all investigators located in the European Economic Area, the sponsor will be responsible for reporting suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities including the European Medicines Agency, investigators, and IRBs/IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. SUSARs will be submitted within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations.

For all other investigators, the sponsor will prepare an expedited report for all SAEs that are unexpected and potentially related to the investigational product, and copies will be distributed to all concerned regulatory authorities, investigator(s), and IRBs/IECs according to applicable laws and regulations. The investigational site also will forward a copy of all expedited reports to the site's applicable IRB/IEC. Investigators must also submit safety information provided by the sponsor to the IRB/IEC as detailed in Section 10.1 and Section 10.2.

6.4.3 Other Events Requiring Immediate Reporting

6.4.3.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information). If the overdose results in an AE, the AE must also be recorded on the AE CRF (see Section 6.3.1). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 6.3.1 and Section 6.4.2).

6.4.3.2 Pregnancy

Pregnancy in a female subject or female partner of a male subject who has received investigational product is required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information).

Subjects who become pregnant during the study must not receive additional doses of investigational product but will not be withdrawn from the study. If the subject requests to know which treatment she received, this information will be provided to her. After obtaining the subject's consent, the pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to MedImmune Patient Safety after outcome. If the partner of a male subject becomes pregnant, her consent will be obtained to follow-up the pregnancy until outcome.

6.4.3.3 Events Meeting Study-stopping Criteria

Events that meet any of the study stopping criteria (Section 3.3), with or without associated AEs or SAEs, are required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information). The occurrence of these events does not automatically make an AE serious, but if the consequences of the event are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 6.3.1 and Section 6.4.2).

6.5 Safety Management During the Study

The MedImmune medical monitor has primary responsibility for the ongoing medical review of safety data throughout the study. This includes review of SAEs and timely review of AEs and "other events" reported during the study. MedImmune Patient Safety is responsible for the receipt, immediate review, investigation, and follow-up of SAEs and other immediately reportable events (eg, overdose and pregnancies) reported from the clinical study sites.

The MedImmune SMC provides safety surveillance, guidance, and oversight for all clinical development studies in which MedImmune has sponsor accountabilities. The SMC members include the heads of Patient Safety, Clinical Development, and Regulatory Affairs, and external physician members with expertise in relevant therapeutic areas. The SMC reviews protocol-specific safety data at regularly scheduled meetings and ad hoc meetings, and provides oversight for individual study protocol safety committees, such as those specified for early-phase dose-escalation studies. Based on review of safety data, the SMC may suspend enrollment or subject dosing in clinical studies, request modification of study documents, or take other actions as deemed necessary.

7 Statistical Considerations

7.1 General Considerations

Two formal analyses (Stage 1 analysis and Stage 2 analysis) and an interim analysis (described in Section 7.4) are planned for the study.

The Stage 1 analysis will be conducted when at least 390 subjects have completed the Week 53 visit; all efficacy and safety data collected through Week 53 will be analyzed. Study site personnel and the subjects will remain blinded to the treatment assignment for individual subjects until the end of the follow-up period to Week 75. MedImmune will be unblinded at the primary analysis.

The Stage 2 analysis for long-term safety follow-up will be performed after all subjects have completed the study.

The PMDA recommends that Japanese subjects should be included in studies in order to identify inter-ethnic differences in the dose-response relationship early in clinical development (PMDA, 2007). Following discussion with PMDA, the target number of

Japanese subjects for inclusion in this study is approximately 65. A subgroup analysis of the Japanese subjects and non Japanese subjects will be performed.

Data will be provided in data listings sorted by treatment group and subject number. Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Confidence intervals (CIs) will be two-sided, unless otherwise stated. Baseline value will be defined as the last valid assessment prior to the first administration of investigational product on Day 1. Details of endpoint analyses, including the multiple comparison adjustment for the primary endpoint analysis will be described in the statistical analysis plan.

7.2 Analysis Populations

The intent-to-treat (ITT) population includes all subjects who are randomized into the study. Treatment arm will be assigned according to the initial randomization, regardless of whether subjects receive any investigational product or receive an investigational product different from that to which they were randomized.

The per protocol (PP) population includes all subjects who have no major protocol violations, complete the treatment period, and have received at least 80% of the intended doses of investigational product during the treatment period.

The safety population includes all subjects who receive any investigational product and have safety data available. The safety analyses will be presented on an as-treated basis.

The evaluable population for PK includes all subjects who receive at least one dose of investigational product and have at least one detectable PK sample.

Detail of each population above and any additional population, if needed, will be described in the Statistical Analysis Plan.

7.3 Endpoints

7.3.1 Primary Endpoint

The primary objective of this study is to evaluate the effect of two SC treatment regimens of 300 mg tralokinumab compared with placebo by assessing the asthma exacerbation rate over 52 weeks in adults with uncontrolled, severe asthma requiring high-dose ICS and LABA with or without additional controller medications. The primary efficacy endpoint is the annual asthma exacerbation rate.

The asthma exacerbation rate will be presented as a weighted mean (total number of exacerbations for the treatment group divided by the total duration of person follow-up) per the joint guidelines recommended by the ATS/ERS. The primary endpoint analysis will be conducted based on the ITT population using a Poisson regression model adjusted for overdispersion with treatment group, age, gender, number of asthma exacerbations in the previous year, and chronic OCS use as potential covariates and the log of number of days in the study as offset. The primary endpoint will also be analyzed using a negative binomial regression model to assess the robustness with regard to the distributional assumptions. Pairwise comparisons between individual tralokinumab treatment group and combined placebo from Cohorts 1 and 2 will be conducted. Comparison between tralokinumab and placebo from the same cohort will be conducted as secondary analyses. Analysis based on the PP population will be performed as a sensitivity analysis.

The primary endpoint will also be analyzed using Cochran-Mantel-Haenszel row Mean Score Test. For analyses based on ITT Population, the adjusted number of exacerbations for subjects who withdraw from the study will be calculated using the following equation: [recorded number of exacerbations] / [number of days in the study] × 365.25.

7.3.2 Secondary Endpoints

7.3.2.1 Safety and Tolerability

The safety of tralokinumab is a secondary objective of this study, which will be assessed by summarizing treatment-emergent AEs and SAEs as well as other safety measurements based on safety population. Treatment-emergent AEs and SAEs will be summarized categorically by system organ class, MedDRA (Medical Dictionary for Regulatory Activities) preferred term, severity, and relationship to investigational product from initiation of investigational

product through Week 75. Other safety assessments include but not limited to physical examination measurement, vital signs, and routine laboratory assessments. These measurements as well as their changes from baseline will be evaluated at each collection time point. In addition, if warranted, shift tables will be included.

7.3.2.2 Effect of Tralokinumab on Pulmonary Function

The effect of tralokinumab on pulmonary function as measured by pre- and post-bronchodilator FEV_1, FEV_6, FVC, and IC at clinic visits (morning); and PEF and FEV_1 measured at home. Change from baseline in the mean values and percent change from baseline at various time points will be summarized using descriptive statistics. Two-sample t-test will be used to compare the changes from baseline and percent changes from baseline in the subject's pulmonary function between the individual tralokinumab treatment group and combined placebo.

7.3.2.3 Effect of Tralokinumab on Patient Reported Outcomes

The change from baseline in the mean ACQ-6 score will be analyzed. The proportion of subjects achieving ACQ-6 ≤ 0.75, ACQ-6 < 1.5, and a reduction from baseline in the mean ACQ-6 score ≥ 0.5 during the study will be compared between the individual tralokinumab treatment group and the combined placebo using the Fisher's exact test. A stratified log-rank test may be conducted to compare the time to first asthma control defined as a reduction from baseline in the mean ACQ-6 score ≥ 0.5 is first observed.

Health-related quality of life will be evaluated using the AQLQ(S) and EQ-5D. The overall and 4 domain scores from the AQLQ(S) responses along with their respective changes from baseline will be summarized using descriptive statistics. Additionally, the proportion of AQLQ(S) responders will be reported; subjects with > 0.5 improvement and subjects with > 1.5 improvement from baseline in AQLQ(S) scores at each visit will be reported separately.

The EQ-5D questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 response options (no problem, some or moderate problems, and unable or extreme problems) that reflect increasing levels of difficulty. The questionnaire also includes a visual analog scale, where the patients are asked to rate their current health on a scale of 0-100, with 0 being the worst imaginable health state. The responses from each dimension and the visual analog scale will be summarized by treatment group and visits. The shift tables will be provided for each

dimension. The change from baseline in visual analog scale will be summarized with descriptive statistics by visit.

7.3.2.4 Effect of Tralokinumab on ASMA Diary and Use of Rescue Medication

The ASMA Diary is a 13-item questionnaire developed by MedImmune and UBC. Subjects are asked to recall their experience with daytime and nighttime symptom frequency and severity, activity avoidance and limitation, asthma-related stress and fatigue as well as rescue medication use. Each item with be summarized showing change over time compared to baseline scores. The number of puffs of rescue medication used will be aggregated over each prior 7-day period and reported and summarized using descriptive statistics. The baseline value for each subject will be defined as the total rescue medication use over the 7 days prior to dosing on Day 1.

7.3.2.5 Pharmacokinetics and Immunogenicity of Tralokinumab

Tralokinumab serum concentrations will be tabulated by treatment group along with descriptive statistics. Serum tralokinumab concentration-time profiles by tralokinumab treatment group will be generated and included in the report. Population modeling may be performed to better characterize the PK of tralokinumab given by SC injection in asthmatic subjects.

The incidence rate of ADA to tralokinumab will be reported by tralokinumab treatment group.

7.3.3 Exploratory Endpoints

Healthcare resource utilization will be evaluated by the number and proportion of subjects who use a healthcare resource by Week 53. Absenteeism, presenteeism, work productivity, and activity impairment for each treatment group will be evaluated with the WPAI-Asthma and will be presented as the proportion of impairment.

By using structural imaging methods based on HRCT, this study will explore possible treatment related changes in airway dimensions. The analysis will be purely exploratory and descriptive statistics will be provided. No formal hypothesis testing will be performed.

The relationship between clinical response and RNA transcript, and serum biomarker profiles will be explored. The analysis will be performed separately by the sponsor.

DNA will also be collected and stored for future exploratory research into genetic variation influencing clinical response to tralokinumab (optional for subjects).

7.4 Interim Analysis

One interim analysis is planned for the study and will be conducted after the last non-Japanese subject randomized into the study has completed the Week 39 visit or discontinued prematurely. All data available will be analyzed as part of the interim analysis.

The overall type I error rate (two-sided) will be controlled at the 0.15 level for the primary endpoint using O'Brien-Fleming alpha spending function based on the actual person-years follow-up observed. For example, if the information fraction at the interim analysis is 88%, then the two-sided type I error rate will be 0.105 for the interim analysis and 0.128 for final analysis, respectively. The interim analysis will have minimal impact on the power of the study at the final analysis, which is estimated to be approximately 78%.

To ensure the blinding of each subject's treatment assignment throughout the study, the interim analysis will be performed by a limited number of sponsor personnel who are not involved in the conduct of the study. Study subjects, site personnel and sponsor personnel directly associated with the conduct of the study will remain blinded to the treatment assignment for individual subjects until the completion of the study.

Details of the interim analysis will be specified in the interim analysis plan prior to unblinding.

7.5 Sample Size and Power Calculations

Sample size calculations have been performed by simulations combined with normal approximation. Simulations assume the data follow exact Poisson distribution. Simulated data have been analyzed using Poisson regression without adjusting for overdispersion.

At least 390 subjects will be randomized in a 1:1 ratio to one of 2 cohorts (Cohorts 1 or Cohort 2). Within each cohort, subjects will be randomized in a 2:1 ratio to receive SC tralokinumab (300 mg) or placebo. The primary analysis will be based on the ITT population.

Fifty-three subjects per treatment arm would be required to detect a 40% reduction in annual asthma exacerbation rate for each tralokinumab cohort compared to placebo assuming an annual exacerbation rate in placebo group of 1.2 with 80% power and a significance level of 0.1. Sample size was increased to 65 per treatment arm to accommodate overdispersion of 1.2. Recent data suggest that approximately half of asthmatic subjects may have a molecularly distinct subtype of asthma characterized by IL-13-driven inflammation; it is reasonable to hypothesize that these IL-13-positive subjects will have the optimal response to tralokinumab therapy. Therefore the sample size has been increased from 65 to approximately 130 subjects per treatment arm to allow for a subanalysis to explore the relationship between the clinical response to tralokinumab and the presence of peripheral blood biomarkers associated with upregulation of IL-13 in the asthmatic lung. In the event that the clinical response is observed only in IL-13-positive subjects, this sample size retains adequate power to detect a difference in the asthma exacerbation rate comparing IL-13-positive tralokinumab treated subjects versus placebo. As presented below, the power to detect a 40% reduction in the exacerbation rate will depend upon the positive predictive value of the peripheral blood biomarker with respect to actual lung IL-13 expression (Table 7.5-1).

Table 7.5-1 Peripheral Blood Biomarker Positive Predictive Value

Peripheral Blood Biomarker PPV	Two-sided alpha	Power (Individual Tralokinumab vs. Placebo)
100%	0.1	81.9%
90%	0.1	73.5%
80%	0.1	61.6%
75%	0.1	57.3%

IL-13 = interleukin-13; PPV = positive predictive value

The accrual of asthma exacerbations is monitored during the study and blinded estimates of the annual asthma exacerbation rate in the placebo group are calculated. These estimates are consistently lower than the planned placebo rate of 1.2 exacerbations per year. In order to maintain adequate power to detect a 40% reduction in the annual asthma exacerbation rate for each tralokinumab cohort compared to placebo, the significance level for the data analysis will be raised from two-sided 0.1 to two-sided 0.15.

Sites in Japan will randomize approximately 65 Japanese subjects as part of the overall sample size. In the event that enrollment of the Japanese subjects is significantly delayed, and to ensure a timely Stage 1 analysis, non-Japanese sites may contribute sufficient subjects to

reach the sample size required for the Stage 1 analysis (at least 390 subjects). In this event, sites in Japan will be permitted to continue enrollment until such time as approximately 65 Japanese subjects have been enrolled. Subgroup analysis of the Japanese subjects for the Stage 1 analysis will be conducted when all subjects have completed the Week 53 visit.

8 Direct Access to Source Documents

The study will be monitored by the sponsor or designee on a regular basis throughout the study period. During monitoring visits, the investigator will provide direct access to all source documentation relevant to the subject's participation in the study. Source documentation includes, but is not limited to, the subject's clinic and/or office chart, hospital chart, informed consent forms, treatment notes, laboratory reports, pharmacy records, radiographs, recorded data from automated instruments, and any other records maintained to conduct and evaluate the clinical study. The investigator must also ensure that direct access to study documents be made available for study-related audits, IRB/IEC review, or regulatory inspection.

9 Quality Control and Quality Assurance

9.1 Data Collection

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate and accurate case histories for the subjects treated under this protocol. Case histories include CRFs and supporting data including, but not limited to, signed and dated informed consent forms, progress notes, hospital charts, nurse's notes, diary cards or other worksheets provided to subjects, laboratory reports, ECG strips, etc.

Subject demographics and key/essential disease baseline characteristics thought to affect outcome, ie, stratification variables and other prognostic factors, may be collected, as available, for all subjects who provide written informed consent. For subjects who provide informed consent and were not entered/randomized into the study, the reason the subject was not entered/randomized, ie, did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (eg, lost to follow-up, consent withdrawn), may also be collected.

9.2 Study Monitoring

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the investigator(s), both the medical record and the research records will be monitored/audited for the purposes of the study.

The investigator and institutions involved in the study will permit study-related monitoring and provide direct access to all study records and facilities. Adequate time and space for monitoring visits should be made by the investigator or other investigator site staff.

The monitor will visit study facilities at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter, to ensure that the study is conducted and documented in accordance with the protocol, Good Clinical Practice (GCP), and applicable regulations. The monitor will assess subject enrollment and informed consent procedures; investigational product storage, dispensing, administration and accountability; compliance with protocol procedures; completeness and accuracy of data entered onto validated data collection instruments (paper CRF or electronic data screen) against original source documents; the continued acceptability of the facilities and qualifications of the site staff; and the occurrence of AEs/SAEs. All aspects of the study will be carefully monitored for compliance with the protocol, applicable regulatory requirements, GCP, and the site's standard operating procedures.

The monitor will discuss the conduct and progress of the study with the investigator and other site staff. The investigator must cooperate with the monitor to ensure that corrective action is taken to resolve any problems noted in the course of the monitoring, and that the preventative measures are put into place to prevent recurrence of issues. In cases where compliance is not achieved, shipment(s) of investigational product to the investigator will be discontinued and study participation by that investigator will be terminated.

9.3 Audit and Inspection of the Study

During and after the study, the sponsor or its representative may conduct audits of any data and any facility participating in the study. The investigator and institutions involved in the study will permit such study-related audits and provide direct access to all study records and facilities. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the sponsor or its designated

monitors, auditors, or regulatory agency representatives. The investigator agrees to participate in audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also perform inspections either during or after the study. In the event of an inspection by any regulatory authority, the investigator should promptly notify the sponsor. The investigator agrees to cooperate fully with inspections conducted by regulatory authorities and to allow representatives of the regulatory authority access to all study records. The investigator will forward to the sponsor a copy of any inspection records received.

10 Ethics

10.1 Regulatory Considerations

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH guidelines on GCP, any applicable laws and requirements, and any conditions required by a regulatory authority and/or IRB/IEC that approves this study to be conducted in its territory. Good clinical practice is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical studies in a way that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study subjects are protected.

Per GCP, the protocol will be reviewed and approved by the IRB or IEC of each participating center prior to study initiation. Serious adverse events regardless of causality will be reported to MedImmune Patient Safety or designee, and the investigator will keep the IRB/IEC informed as to the progress of the study.

The investigator will explain the nature of the study and will inform the subject that participation is voluntary and that the subject can withdraw or be withdrawn from the study at any time. Written informed consent will be obtained from each subject prior to the screening procedures to determine if study eligibility criteria are met. A copy of the signed consent form(s) will be given to every subject, and the original(s) will be maintained with the subject's records.

10.2 Institutional Review Board or Independent Ethics Committee

A list of IRB/IEC members or a Statement of GCP Compliance should be obtained by the investigator and provided to the sponsor.

Any documents that the IRB/IEC may need to fulfill its responsibilities, such as protocol amendments, and information concerning subject recruitment, payment, or compensation procedures, or information from the sponsor will be submitted to the IRB/IEC. The IRB/IEC's written unconditional approval of the study protocol, the informed consent form(s), and any other written materials to be provided to subjects will be in the possession of the investigator and the sponsor before the study is initiated. The IRB/IEC's unconditional approval statement will be transmitted by the investigator to the sponsor prior to shipment of investigational product supplies to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and the date of review.

Protocol modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted should be obtained.

The IRB/IEC must be informed by the investigator of informed consent form changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study (as applicable according to local regulations); new information that may affect adversely the safety of the subjects or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

10.3 Informed Consent

Freely given informed consent will be obtained and documented for all subjects under this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH guidelines on GCP, any applicable laws and requirements, and any conditions required by a Regulatory Authority and/or IRB/IEC.

Information should be given in both oral and written form, and subjects must be given ample opportunity to inquire about details of the study. Written informed consent will additionally be obtained for the conduct of certain protocol-specified procedures. If the study will enroll subjects who are unable to give written informed consent, such as children or incapacitated subjects, informed consent will be obtained according to the site's standard operating procedures.

The consent form(s) generated by the investigator must be approved by the IRB/IEC and be acceptable to the sponsor. Consent forms must be written so as to be understood by the prospective subject. Informed consent will be documented by the use of a written consent form(s) approved by the IRB/IEC and signed and dated by the subject, and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form(s) must be kept on file by the investigator for possible inspection by the sponsor or its designated monitors, auditors, or regulatory agency representatives. The subject should receive a copy of the signed and dated written informed consent form(s) and any other written information provided to the subject, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

10.4 Withdrawal of Consent for Continued Study Participation

Data and Samples Obtained for the Main Study

Study data are protected by the use of a subject identification number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any data collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

Samples Obtained for Genetic Research or Future Research

Samples obtained for genetic research or future research will be labeled with a sample identification number but will not be labeled with personal identifiers such as the subject's name. A file linking this sample identification number with the subject identification number will be kept in a secure place at the sponsor with restricted access. If the subject withdraws

consent for participating in the genetic research or future research, this link will allow the sponsor to locate the subject's sample and destroy it. The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

If the subject consents to have his/her samples used for genetic research or future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) including any specimens of extracted DNA will be stored by the sponsor with similar samples from other subjects at a secure central laboratory. The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for genetic research or future research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

If consent is withdrawn after a sample has been taken but before the subject's sample is sent to the sponsor for genetic research or future research, the investigator will arrange to have it destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the sponsor for genetic research or future research, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the sample identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's samples have already been used for research, the sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

11 Data Handling and Record Keeping

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a subject's identification number or coded number and age. All study records, source medical records, and code sheets or logs linking a subject's name to an SID number will be kept in a secure location. Study records such as CRFs may be maintained electronically and require the same security and confidentiality as paper. Clinical information will not be released without written permission of the subject, except as specified in the informed consent form(s) (eg, necessary for monitoring by regulatory authorities or the sponsor of the clinical study). The investigator must also comply with all applicable privacy regulations (eg, HIPAA 1996, EU Data Protection Directive 95/46/EC).

Study documents (including subject records, copies of data submitted to the sponsor, study notebook, and pharmacy records) must be kept secured in accordance with the specific data retention periods that are described in the clinical study site agreement and based upon local requirements. Study documents must not be destroyed without prior written approval of the sponsor.

12 Financing and Insurance

Financing and insurance are addressed in the individual site contracts.

13 Publication Policy

Publication by the site of any data from this study must be carried out in accordance with the clinical study site agreement.

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15 Summary of Protocol Amendments and Administrative Changes to the Protocol

15.1 Administrative Change 1, [redacted]

The purpose of this administrative change is to correct the EudraCT number presented on the title page of the protocol. The correct EudraCT number reads 2011-001360-21.

15.2 Protocol Amendment 1, [redacted]

Text revisions resulting from this amendment are incorporated into the body of Protocol Amendment 1. Major changes to the protocol are summarized below:

1) Section 3.1 Overview of Study Design, the phrase “a total of 390 subjects” was replaced with “at least 390 subjects” to allow additional subjects into the study who

were in the 5-week screening/run-in period at the time 390 subjects had been randomized into the study. This section also stipulated that approximately 65 Japanese subjects would be included in the study.

2) Section 3.3 Study-stopping Criteria, the text has been amended to provide further clarity on the process that will be followed and to clarify the study-stopping criteria.

3) Section 3.4.1 Study Rationale and Choice of Study Population, this section was updated to include the PMDA rationale for adding approximately 65 Japanese subjects into the study.

4) Section 4.2.1 Inclusion Criteria, criterion 4 has been amended to include mannitol as another challenge agent that may be used to demonstrate the presence of airway hyperresponsiveness since this is used as an accepted method in certain regions where this study is being conducted.

5) Section 4.2.1 Inclusion Criteria, criterion 7 has been amended to include secondary ICS as another example of other asthma controller medication.

6) Section 4.2.1 Inclusion Criteria, criterion 10 has been updated to remove the word run-in to be consistent with the wording in Section 5.2.3 Chest X-ray for Screening.

7) Section 4.2.1 Inclusion Criteria, criterion 15 has been clarified to make the name of the diary clear; ie, ASMA (Assessing Symptoms of Moderate-to-severe Asthma) diary.

8) Section 4.2.2 Exclusion Criteria, criterion 10 has been modified for accuracy since all live vaccines are live attenuated. Criterion 11 has been clarified to include the dose of prednisolone or equivalent OCS that is exclusionary. Criterion 12 has been clarified to refer to the excluded medications in Section 4.6.2. Criterion 16 has been clarified to define that subjects should have stopped smoking for at least 3 months prior to screening.

9) Section 4.2.3 Withdrawal Criteria, text has been added to indicate that subjects should undertake the follow-up visits if they do not complete the treatment period, unless consent is withdrawn.

10) Section 4.2.4 Replacement of Subjects, the text has been amended to allow for any subjects randomized in error to be replaced at the discretion of the medical monitor; this allows the sample size of eligible subjects to be maintained.

11) Section 4.3 Treatment Assignment, text has been added to clarify that any eligible subject remaining in the 5-week screening/run-in period at the time 390 subjects have been randomized into the study will also be randomized into the study. Having consented to participate in the study and successfully qualified, this is considered appropriate.

12) Section 4.5.2.1 Background Medication, the text has been amended to allow for subjects who require a secondary ICS in addition to the fixed dose combination product of fluticasone/salmeterol, and to clarify the inclusion of oral prednisolone ≤ 20 mg/day or equivalent OCS.

13) Section 4.6.1 Permitted Concomitant Medications, text has been added to this section to state the minimum period that should separate the administration of investigational product and allergen-specific immunotherapy.

14) Section 5.1.1 Screening/Run-in Period has been amended to include further clarity on the process that will be followed in the event that repeat screening assessments are required.

15) Section 5.1.1.3 Week -2 (Day -14 plus/minus 3 days): Run-in (Visit 3) has been updated to remove urinalysis in order to be consistent with the Schedule of Study Procedures, Table 5.1-1. Urinalysis is not performed at this visit.

16) Section 5.1.2 Treatment Period has been amended to include a description of the time windows allowed for scheduled study visits. Sections 5.1.2.5, 5.1.2.7, 5.1.2.10, 5.1.2.16, 5.1.2.19, and 5.1.2.25 have been amended to clarify that the blood samples collected on the day of dosing should be predose.

17) Section 5.1.2.27 Unscheduled Dosing Visit, the facility to undertake an unscheduled dosing visit has been added to ensure that investigators can prevent the occurrence of prolonged periods between administrations of investigational product that would potentially threaten the study objectives.

18) Section 5.2.3 Chest X-ray for Screening, the requirement to have both an anterior/posterior and lateral chest x-ray has been removed since an anterior/posterior view will be adequate in most cases and will be left to the discretion of the investigator.

19) Section 5.2.5 Measurement of Theophylline Levels, text has been clarified since the theophylline levels measured during this study will not be peak levels. The results obtained during the study will however ensure that subjects do not have serum theophylline levels that exceed the established safe range.

20) Section 5.2.10.3 Spirometry, text has been added to describe the method employed to record inspiratory capacity and Table 5.2.10.3-1 has been clarified to make it clear that theophylline is not the only oral bronchodilator permitted.

21) Section 5.2.10.6 Computed Tomography, text has been modified to make it clear that HRCT using the spiral scanning mode will be used in this study.

22) Section 5.2.11.1 Asthma Control Questionnaire and Section 7.3.2.3 Effect of Tralokinumab on Patient Reported Outcomes, the ACQ cut-point for uncontrolled asthma was incorrectly listed as > 1.5 and has been updated with the correct cut-point of ≥ 1.5.

23) Section 6.4.3.2 Pregnancy was revised to include a female partner of a male subject.

24) Section 7.1 General considerations, following consultation with the Japanese Agency (PMDA) text has been added to introduce the requirement to enroll approximately 65 subjects from Japan.

25) Section 7.3.1 Primary Endpoint, chronic OCS use has been added as a potential covariate.

26) Section 7.5 Sample Size and Power Calculations, text was revised to include the approximately 65 Japanese subjects as part of the overall sample size. This section also stipulated that if the enrollment of Japanese subjects is significantly delayed, non-Japanese sites may contribute sufficient subjects to reach the required sample size of 390 subjects for the Stage 1 analysis.

15.3 Protocol Amendment 2, [redacted]

Text revisions resulting from this amendment are incorporated into the body of Protocol Amendment 2. Major changes to the protocol are summarized below:

1) Study Abstract and Section 7.5 have been amended to describe an increased alpha significance level for the primary endpoint. The accrual of asthma exacerbations is monitored during the study and blinded estimates of the annual asthma exacerbation rate in the placebo group are calculated. These estimates are consistently lower than the planned placebo rate of 1.2 exacerbations per year. In order to maintain adequate power to detect a 40% reduction in the annual asthma exacerbation rate for each tralokinumab cohort compared to placebo, the significance level for the data analysis will be raised from two-sided 0.1 to two-sided 0.15.

2) Sections 5.1.2.5, 5.1.2.7, 5.1.2.9, 5.1.2.10, 5.1.2.11, 5.1.2.13, 5.1.2.15, 5.1.2.16, 5.1.2.19, 5.1.2.21, and 5.1.2.25; text has been added to be consistent with the timing of the postdose vital sign assessments described in Section 5.2.2.1. This is not a change to the protocol.

3) Section 5.1.2.6; Text has been added to correctly list the assessments to be performed at this visit to make it consistent with those listed in Table 5.1-2.

4) Sections 5.1.2.8, 5.1.2.12, 5.1.2.14, 5.1.2.18, 5.1.2.20, 5.1.2.22, 5.1.2.24, and 5.1.2.26 have been corrected so that it is stated that assessments should be performed as for Week 11, Visit 9.

5) Sections 4.5.4 and 5.2.7 has been amended to clarify that the time of the first SC injection is recorded for each subject.

6) Section 6.5 has been amended to reflect a change in the members of the MedImmune SMC.

7) Section 7.2 has been amended to describe the evaluable population for PK to include all subjects who receive at least one dose of investigational product and have at least one detectable PK sample. Pharmacokinetic parameters will not be computed for the clinical study report because of the sparse sampling PK scheme. The description of the per protocol was also clarified to include all subjects who have no major protocol violations, complete the treatment period, and have received at least 80% of the intended doses of investigational product during the treatment period.

15.4 Protocol Amendment 3, [redacted]

Text revisions resulting from this amendment are incorporated into the body of Protocol Amendment 3. Major changes to the protocol are summarized below:

1) Title Page: Changed medical monitor from [redacted] to [redacted]

2) Section 4.4 (Blinding) and Section 7.1 (General Considerations) was amended to include the conduct of one interim analysis as a formal analysis. The sentence "The primary analysis for which the study is powered will be completed in the Stage 1 analysis, and no new analyses based on primary efficacy endpoint will be made at the end of the study; therefore, no multiplicity adjustment will be applied" was deleted for clarity due to the inclusion of an interim analysis.

3) Section 4.4.2 (Unblinding for Interim Analysis Purposes) was added to describe the unblinding procedures for the interim analysis.

4) Section 7.3.1 (Primary Endpoint) was amended to confirm the definition of the primary efficacy endpoint.

5) Section 7.4 (Interim Analysis) was amended to include the conduct of one interim analysis after the last non-Japanese subject randomized into the study has completed the Week 39 visit or discontinued prematurely. All data available at the time of the interim analysis will be analyzed. The overall objective of this analysis is to allow an early assessment of the efficacy and tolerability of tralokinumab to enable strategic planning for future development this molecule.

   The conduct of the interim analysis has been carefully considered to ensure the integrity of the study is not compromised. The analysis will be performed by a limited number of sponsor personnel who are not involved in the conduct of the study to maintain the blinding of each subject's treatment assignment and appropriate statistical analysis techniques will be used to account for multiplicity to ensure that the overall alpha is controlled at the 0.15 level for the primary endpoint (using O'Brien and Fleming alpha spending method).

   The interim analysis will have minimal impact on the power of the study at the final efficacy analysis, which is estimated to be approximately 78%. Adequate power to detect a 40% reduction in the annual asthma exacerbation rate for each tralokinumab cohort compared to placebo will be maintained to fulfill the study objective.

Appendix 1 Signatures

Sponsor Signature

A Phase 2b, Randomized, Double-blind Study to Evaluate the Efficacy of Tralokinumab in Adults with Uncontrolled, Severe Asthma

I agree to the terms of this protocol amendment.

Signature and date: [redacted]

Sponsor Signature

A Phase 2b, Randomized, Double-blind Study to Evaluate the Efficacy of Tralokinumab in Adults with Uncontrolled, Severe Asthma

I agree to the terms of this protocol amendment.

Signature and date: [redacted]

Sponsor Signature

A Phase 2b, Randomized, Double-blind Study to Evaluate the Efficacy of Tralokinumab in Adults with Uncontrolled, Severe Asthma

I agree to the terms of this protocol amendment.

Signature and date: [redacted]

Signature of Coordinating Investigator

A Phase 2b, Randomized, Double-blind Study to Evaluate the Efficacy of Tralokinumab in Adults with Uncontrolled, Severe Asthma

I, the undersigned, have reviewed this protocol amendment, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: [redacted]

Name and title: [redacted]

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available or applicable) _____

Signature of Principal Investigator

A Phase 2b, Randomized, Double-blind Study to Evaluate the Efficacy of Tralokinumab in Adults with Uncontrolled, Severe Asthma

I, the undersigned, have reviewed this protocol amendment, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

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Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available) _____

Appendix 2 Acceptable Doses of Inhaled Corticosteroids in the 30 days before Screening

Acceptable Doses of High-dose ICS in the 30 days before Screening

ICS	Daily Dose (µg)
Beclometasone Beclometasone HFA	> 1000 > 480
Budesonide	> 800
Ciclesonide	> 320
Flunisolide Flunisolide (HFA)	> 2000 > 640
Fluticasone Fluticasone (HFA)	> 500 > 440
Mometasone	> 400
Triamcinolone	> 1500

HFA = hydrofluoroalkane-134a; ICS=inhaled corticosteroids
Source: GINA, 2009; EPR3, 2007

Appendix 3 Global Initiative for Asthma: Approach to Asthma Control

Stepwise Approach to Asthma Control for Children Older than 5 years, Adolescents and Adults

Step 1	Step 2	Step 3	Step 4	Step 5
Asthma education/ Environmental control				
As needed rapid-acting β_2-agonist	As needed rapid-acting β_2-agonist			
Controller options***	Select one	Select one	To Step 3 treatment, add one or more	To Step 4 treatment, add either
	Low-dose inhaled ICS*	**Low-dose ICS plus LABA**	**Medium-or high-dose ICS plus LABA**	Oral glucocorticosteroid (lowest dose)
	Leukotriene modifier**	Medium-or high-dose ICS	Leukotriene modifier	Anti-IgE treatment
		Low-dose ICS plus leukotriene modifier	Sustained release theophylline	
		Low-dose ICS plus sustained release theophylline		

LABA - long-acting β_2-agonist

*ICS - inhaled glucocorticosteroids

** - Receptor antagonist or synthesis inhibitors

***Preferred controller options are in bold

Adapted from GINA 2009

Appendix 4 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 (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING

   a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

   b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

2) Two or more of the following that occur rapidly after exposure to a <u>likely</u> allergen for that subject (minutes to several hours):

   a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).

   b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

   c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).

   d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

3) Reduced BP after exposure to <u>known</u> allergen for that subject (minutes to several hours): Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that subject'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.

Appendix 5 Signs and Symptoms and Management of Acute Anaphylaxis

Signs and Symptoms 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

Management of Acute Anaphylaxis

I. Immediate intervention

a. Assessment of airway, breathing, circulation, and adequacy of mentation

b. 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.

II. 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.

III. Specific measures to consider after epinephrine injections, where appropriate

a. Consider epinephrine infusion.

b. Consider H1 and H2 antihistamines.

c. Consider nebulized β2 agonist [eg, 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.

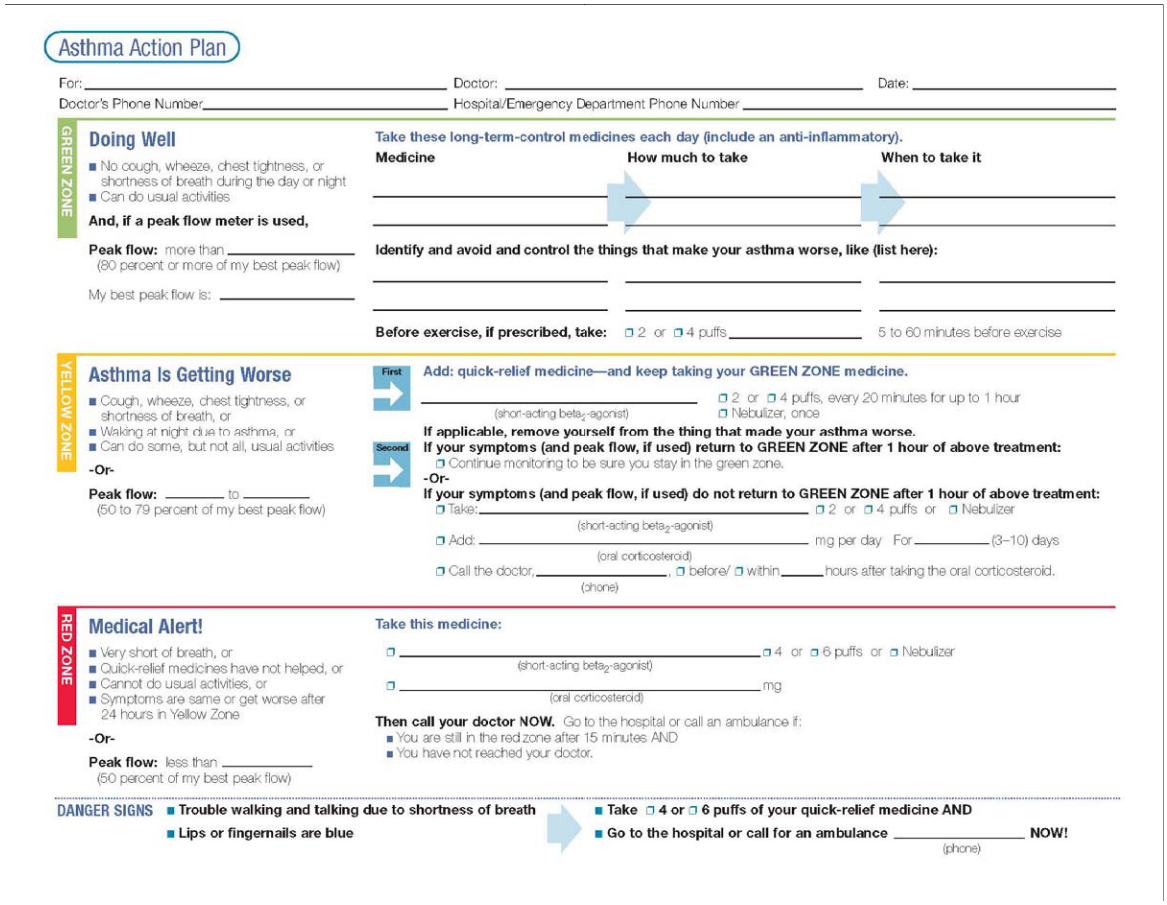
Appendix 6 Factors Affecting Clearance of Theophylline

Factors Affecting Clearance of Theophylline

Increased Clearance
Enzyme induction (rifampicin, phenobarbitone, ethanol)
Smoking (tobacco, marijuana)
High protein, low carbohydrate diet
Barbecued meat
Childhood
Decreased Clearance
Enzyme inhibition (cimetidine, erythromycin, ciprofloxacin, allopurinol, zileuton, zafirlukast)
Congestive heart failure
Liver disease
Pneumonia
Viral infection and vaccination
High carbohydrate diet
Old age

Adapted from Harrison's Principles of Internal Medicine, 17th Edition, New York: McGraw-Hill Medical Publishing Division. 2008.

Appendix 7 Example of Personalized Asthma Action Plan



Asthma Action Plan

For: _____ Doctor: _____ Date: _____

Doctor's Phone Number: _____ Hospital/Emergency Department Phone Number _____

GREEN ZONE

Doing Well

- No cough, wheeze, chest tightness, or shortness of breath during the day or night
- Can do usual activities

And, if a peak flow meter is used,

Peak flow: more than _____ (80 percent or more of my best peak flow)

My best peak flow is: _____

Take these long-term-control medicines each day (include an anti-inflammatory).

Medicine	How much to take	When to take it

Identify and avoid and control the things that make your asthma worse, like (list here):

Before exercise, if prescribed, take: ❒ 2 or ❒ 4 puffs _____ 5 to 60 minutes before exercise

YELLOW ZONE

Asthma Is Getting Worse

- Cough, wheeze, chest tightness, or shortness of breath, or
- Waking at night due to asthma, or
- Can do some, but not all, usual activities

-Or-

Peak flow: _____ to _____ (50 to 79 percent of my best peak flow)

First

Add: quick-relief medicine—and keep taking your GREEN ZONE medicine.

_____ (short-acting beta$_2$-agonist) ❒ 2 or ❒ 4 puffs, every 20 minutes for up to 1 hour ❒ Nebulizer, once

Second

If applicable, remove yourself from the thing that made your asthma worse.

If your symptoms (and peak flow, if used) return to GREEN ZONE after 1 hour of above treatment:

❒ Continue monitoring to be sure you stay in the green zone.

-Or-

If your symptoms (and peak flow, if used) do not return to GREEN ZONE after 1 hour of above treatment:

❒ Take: _____ (short-acting beta$_2$-agonist) ❒ 2 or ❒ 4 puffs or ❒ Nebulizer

❒ Add: _____ (oral corticosteroid) mg per day For _____ (3–10) days

❒ Call the doctor, _____ (phone), ❒ before/ ❒ within _____ hours after taking the oral corticosteroid.

RED ZONE

Medical Alert!

- Very short of breath, or
- Quick-relief medicines have not helped, or
- Cannot do usual activities, or
- Symptoms are same or get worse after 24 hours in Yellow Zone

-Or-

Peak flow: less than _____ (50 percent of my best peak flow)

Take this medicine:

❒ _____ (short-acting beta$_2$-agonist) ❒ 4 or ❒ 6 puffs or ❒ Nebulizer

❒ _____ (oral corticosteroid) mg

Then call your doctor NOW. Go to the hospital or call an ambulance if:

- You are still in the red zone after 15 minutes AND
- You have not reached your doctor.

DANGER SIGNS

- **Trouble walking and talking due to shortness of breath**
- **Lips or fingernails are blue**

- **Take ❒ 4 or ❒ 6 puffs of your quick-relief medicine AND**
- **Go to the hospital or call for an ambulance _____ (phone) NOW!**

Appendix 8 Patient Reported Outcomes Questionnaires

Asthma Control Questionnaire, 1997

Asthma Quality of Life Questionnaire with Standardised Activities, 1996

Assessing Symptoms of Moderate-to-severe Asthma Diary

ASMA Diary Anchor Questions

EQ-5D, EuroQol Group 1990

Work Productivity and Activity Impairment Questionnaire Asthma

Healthcare Resource Utilisation

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

For further information:

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MAY 1997

MODIFIED DECEMBER 2007 FOR MEDIMMUNE
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Protocol MI-CP_ _ _ For Subject Completion ONLY PID _ _ _ _ _ _ _

Visit _ _ CONFIDENTIAL Date _ _/____/_ _ _ _ (DD/MON/YEAR)

Subj Initials _ _ _

ASTHMA CONTROL QUESTIONNAIRE© SELF-ADMINISTERED

Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?
   - 0 None
   - 1 A very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 A very great deal

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ASTHMA CONTROL QUESTIONNAIRE© SELF-ADMINISTERED

5.	In general, during the past week, how much time did you **wheeze?**	0	Never
		1	Hardly any of the time
		2	A little of the time
		3	A moderate amount of the time
		4	A lot of the time
		5	Most of the time
		6	All the time
6.	On average, during the past week, how many **puffs/inhalations of short-acting bronchodilator** (eg. Ventolin/Bricanyl) have you used each day? *(If you are not sure how to answer this question, please ask for help)*	0	None
		1	1 - 2 puffs/inhalations most days
		2	3 - 4 puffs/inhalations most days
		3	5 - 8 puffs/inhalations most days
		4	9 - 12 puffs/inhalations most days
		5	13 - 16 puffs/inhalations most days
		6	More than 16 puffs/inhalations most days

To be completed by a member of the clinic staff

7.	FEV_1pre-bronchodilator:	0	> 95% predicted
		1	95 - 90%
	FEV_1predicted:	2	89 - 80%
		3	79 - 70%
	FEV_1%predicted:	4	69 - 60%
	(Record actual values on the dotted lines and score the FEV_1 % predicted in the next column)	5	59 - 50%
		6	< 50% predicted

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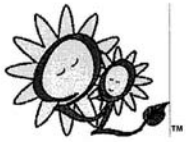
ASTHMA QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (AQLQ(S))

SELF-ADMINISTERED



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JUNE 1998

MODIFIED NOVEMBER 2007 FOR MEDIMMUNE
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ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) SELF-ADMINISTERED

Please complete **all** the questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

HOW **LIMITED** HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK-RELATED ACTIVITIES (tasks you have to do at work*)	1	2	3	4	5	6	7
**If you are not employed or self-employed, these should be tasks you have to do most days.*							
5. SLEEPING	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

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ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) SELF-ADMINISTERED

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7

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ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) SELF-ADMINISTERED

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

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Protocol MI-CP_ _ _ For Subject Completion ONLY PID _ _ _ _ _ _ _

Visit _ _ CONFIDENTIAL Date _ _ /____/_ _ _ _ (DD/MON/YEAR)

Subj Initials _ _ _

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) SELF-ADMINISTERED

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
27. Feel AFRAID OF GETTING OUT OF BREATH?	1	2	3	4	5	6	7
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has you asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
30. Have the feeling of FIGHTING FOR AIR?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Most Not Done		Several Not Done		Very Few Not Done		No Limitation
31. Think of all the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks? How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

MODIFIED NOVEMBER 2007 FOR MEDIMMUNE
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Protocol MI-CP_ _ _ For Subject Completion ONLY PID _ _ _ _ _ _ _

Visit _ _ CONFIDENTIAL Date _ _/___/_ _ _ _
(DD/MON/YEAR)

Subj Initials _ _ _

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) SELF-ADMINISTERED

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at All Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

DOMAIN CODE:

Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function: 7, 13, 15, 21, 27
Environmental Stimuli: 9, 17, 23, 26

MODIFIED NOVEMBER 2007 FOR MEDIMMUNE
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MedImmune Tralokinumab
Assessing Symptoms of Moderate-to-Severe Asthma (ASMA) Diary v1.1

Instructions: Please complete ALL questions by selecting the response that best describes your asthma. Asthma symptoms could include shortness of breath, wheezing, coughing, and/or chest tightness.

DAYTIME SYMPTOMS:

The following questions ask about your asthma during the daytime yesterday. Daytime refers to the period of time from when you woke up until the time you went to sleep yesterday.

1. How often did you experience asthma symptoms (shortness of breath, wheezing, coughing, and/or chest tightness) during the daytime yesterday?

- ☐ None of the time
- ☐ A little of the time
- ☐ Some of the time
- ☐ Most of the time
- ☐ All of the time

2. How severe were your asthma symptoms during the daytime yesterday?

- ☐ No asthma symptoms
- ☐ Mild symptoms
- ☐ Moderate symptoms
- ☐ Severe symptoms
- ☐ Most severe symptoms imaginable

3. Did you use rescue medication (inhaler or nebulizer) in response to **worsening symptoms** during the daytime yesterday?

- ☐ No
- ☐ Yes

3a. How many **times** did you use rescue medication in response to worsening symptoms during the daytime yesterday? For example, multiple puffs of your inhaler taken together or a single use of your nebulizer would be ONE time.

4. Did you use rescue medication (inhaler or nebulizer) **before having symptoms** (such as before doing housework or exercise) during the daytime yesterday?

- ☐ No
- ☐ Yes

4a. How many **times** did you use rescue medication before symptoms during the daytime yesterday? For example, multiple puffs of your inhaler taken together or a single use of your nebulizer would be ONE time.

MedImmune — Tralokinumab
Assessing Symptoms of Moderate-to-Severe Asthma (ASMA) Diary — v1.1

NIGHTTIME SYMPTOMS:

The following questions ask about your asthma symptoms last night. Last night refers to the period of time from when you went to sleep yesterday until the time you woke up today.

5. Did your asthma cause you to wake up last night?
   - ☐ No
   - ☐ Yes

6. How severe were your asthma symptoms last night?
   - ☐ No asthma symptoms
   - ☐ Mild symptoms
   - ☐ Moderate symptoms
   - ☐ Severe symptoms
   - ☐ Most severe symptoms imaginable

7. Did you use rescue medication (inhaler or nebulizer) last night?
   - ☐ No
   - ☐ Yes

   7a. How many **times** did you use rescue medication last night? For example, multiple puffs of your inhaler taken together or a single use of your nebulizer would be ONE time.

PREVIOUS 24 HOURS

The following questions ask about your asthma during the past 24 hours.

8. Did you experience an asthma attack during the past 24 hours?
   - ☐ No
   - ☐ Yes

9. Did you feel stressed because of your asthma during the past 24 hours?
   - ☐ Yes
   - ☐ No

10. How often did you feel tired during the past 24 hours?
   - ☐ None of the time

- ☐ A little of the time
- ☐ Some of the time
- ☐ Most of the time
- ☐ All of the time

11. How limited were your activities as a result of your asthma during the past 24 hours?
- ☐ Not at all limited
- ☐ Slightly limited or a little limited
- ☐ Moderately limited
- ☐ Very limited
- ☐ Totally limited

12. How often did you have to avoid activities because of your asthma during the past 24 hours?
- ☐ None of the time
- ☐ A little of the time
- ☐ Some of the time
- ☐ Most of the time
- ☐ All of the time

13. How often did you have to pace yourself during activities because of your asthma during the past 24 hours?
- ☐ None of the time
- ☐ A little of the time
- ☐ Some of the time
- ☐ Most of the time
- ☐ All of the time

Assessing Symptoms of Moderate-to-Severe Asthma (ASMA) Diary Anchor Questions
Version 1.1

Please answer the following questions.

1. How would you rate your asthma symptoms over the past 7 days?

None, Minimal, Mild, Moderate, Severe

2. How often did you experience daytime asthma symptoms over the past 7 days?

Never, Almost Never, Sometimes, Fairly Often, Very Often

3. How severe were your daytime asthma symptoms over the past 7 days?

Not at all, Slightly, Moderately, Very, Extremely

4. How severe were your nighttime asthma symptoms over the past 7 days?

Not at all, Slightly, Moderately, Very, Extremely

5. How often did you use your rescue medication over the past 7 days?

Never, Almost Never, Sometimes, Fairly Often, Very Often

6. Considering things like your asthma symptoms, nighttime awakenings, rescue medication use and impact on activities in the past 7 days, how would you rate your asthma overall?

No problems, minimal, mild, moderate, severe, very severe

7. How would you rate your asthma over the past 7 days compared with how you felt before you entered the study?

Much worse, Moderately worse, A little worse, About the same - hardly any change at all, A little better, Moderately better, Much better

English U.S.

Health Questionnaire

(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

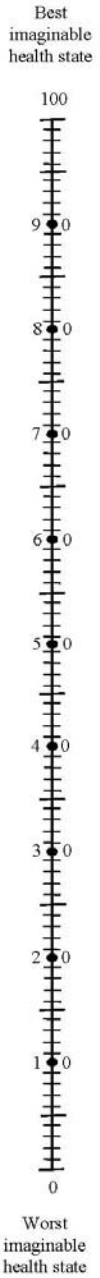
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



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Work Productivity and Activity Impairment Questionnaire:
ASTHMA (WPAI:Asthma)

The following questions ask about the effect of your asthma on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your asthma? *Include hours you missed on sick days, times you went in late, left early, etc., because of your asthma. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your asthma affect your productivity <u>while you were working</u>?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If asthma affected your work only a little, choose a low number. Choose a high number if asthma affected your work a great deal.

Consider only how much <u>asthma</u> affected productivity <u>while you were working</u>.

Asthma had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Asthma completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your asthma affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If asthma affected your activities only a little, choose a low number. Choose a high number if asthma affected your activities a great deal.

Consider only how much <u>asthma</u> affected your ability to do your regular daily activities, other than work at a job.

Asthma had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Asthma completely prevented me from doing my daily activities

CIRCLE A NUMBER

Healthcare Resource Utilization Questions for the eDiary

Weekly assessments

How many phone calls did you have with a healthcare provider due to your asthma in the previous week? Please do not include phone calls to your study site.

How many physician office visits did you have due to your asthma in the previous week? Please do not include study site visits.

How many urgent care or emergency department visits did you have due to your asthma in the previous week?

Were you hospitalized due to your asthma in the previous week?

Yes
No