Statistical Analysis Plan

Protocol Number: CD-RI-CAT-354-1049/ D2210L00001

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 (Standardized 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
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
FSH	follicle-stimulating hormone
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
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
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
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

1 Introduction

This document describes the statistical methodology for CD-RI-CAT-354-1049/ D2210L00001, a Phase 2b, Randomized, Double-blind Study to Evaluate the Efficacy of Tralokinumab in Adults with Uncontrolled, Severe Asthma. Some background information and an overview of the study design are provided in Section 2. Section 3 and onwards of the document details the statistical summaries relating to each study objective as well as describing general conventions and definitions. A separate statistical programming plan (SPP), containing table templates and specifications, has also been created to be used in conjunction with this document.

2 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.

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)

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.

2.1 Study Overview

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 100 sites around the world will participate in the study. A total of approximately 390 subjects will be randomized in a 1:1 ratio to one of 2 cohorts (Cohort 1 or Cohort 2). 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). To maximize the probability of obtaining treatment balance within Japanese population for the purpose of PMDA filing, the Japanese will be randomized separately.

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, chromones, or OCS ≤ 20 mg/day), 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 (e.g., SABA or short-acting anticholinergic) on an as-required basis as documented in their Personalized Asthma Action Plan.

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 treatment groups for the HRCT substudy.

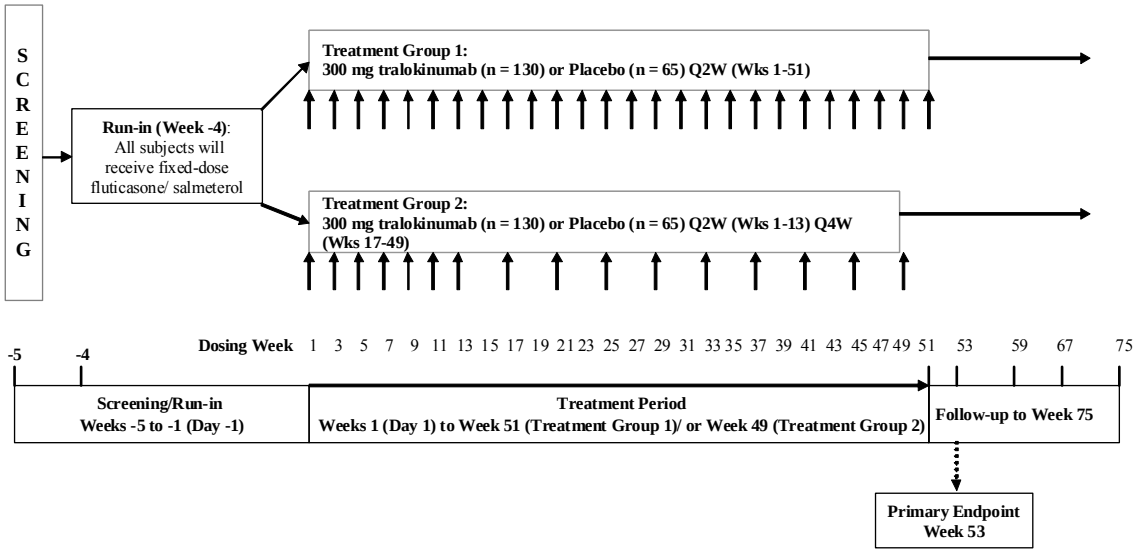

Figure 2.1-1 Study Flow Diagram

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

2.2 Randomization and Blinding

2.2.1 Subject Randomization Procedures and Treatment Allocation

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 the number of asthma exacerbations in the past year (2 versus > 2 but ≤ 6 exacerbations) and by chronic OCS use (presence versus absence). To maximize the probability of obtaining treatment balance within Japanese population for the purpose of PMDA filing, the Japanese will be randomized separately.

2.2.2 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) as well as an interim analysis will be performed for the study. The Stage 1 analysis will be conducted after the last subject has completed the Week 53 visit. The Stage 2 analysis for long-term safety follow-up will be performed after all subjects have completed the study. 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 Stage 1 primary analysis.

The interim analysis will be performed by a limited number of sponsor personnel who are not involved in the conduct of the study.

2.3 Sample Size Considerations

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.

A total of 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 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 1).

Table 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.

3 Statistical Methods

3.1 General Considerations

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 for the overall population will be conducted after the last non-Japanese subject has completed the Week 53 visit or discontinued prematurely (this analysis will include all Japanese subjects who have completed Week 53). The Stage 2 analysis for long-term safety follow-up will be performed after all subjects have completed the study or discontinued prematurely. During the Stage 1 analysis, all the efficacy and safety data

collected will be analyzed. Pairwise comparisons between individual tralokinumab treatment groups and combined placebo will be conducted. The primary analysis for which the study is powered will be completed in the Stage 1 analysis, and the analyses based on primary efficacy endpoint will be repeated for overall population (which includes all subjects enrolled into the study) at the end of the study as sensitivity analysis.

The interim analysis 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 details of the interim analysis will be specified in unblinding plan for 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%.

Three sets of analyses will be performed at Stage 1. They are: 1) analyses based on overall population; 2) analyses for Japan only subjects (n=45); and 3) analyses for non-Japanese subjects. The go/no-go decision will be based on stage 1 analysis for overall population.

In addition, for PMDA consultation, the same analyses for all Japan subjects (n=64) will be conducted when all Japan subjects complete week 53 follow-up or discontinue prematurely.

The academic collaborations to identify serum biomarker(s) are on-going, separate analyses for subgroups classified by the lead candidate(s) will be performed according to the exploratory analysis plan (EAP). The family-wise error rate (FWER) toward the analyses of the primary endpoint of the current study will be controlled through Hochberg step-up procedure.

All data related to various study endpoints will be provided in data listings sorted by treatment group (tralokinumab Q2W, tralokinumab Q2W/Q4W, and placebo), subject number, and study visit. Summary data will be presented in tabular format 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 N, mean, standard deviation, median, and range. The 85% confidence intervals (CIs) will be two-sided unless otherwise stated.

Day 1 value prior to study drug administration is used for baseline. If the Day 1 value is missing or is invalid or is after study drug administration, the baseline should be determined as the latest assessment within two weeks prior to Day 1. The change from baseline is computed as (visit value – baseline value). Percent change from baseline is computed as ((visit value – baseline value)/baseline value) × 100. If either a visit value or the baseline visit value is missing, the change from baseline value and the percent change from baseline will also be set to missing. If a visit value is non-zero, while the baseline visit value is zero, the change from baseline value will be computed but the percent change from baseline will be regarded as undefined (missing value) and will not be included in computation of the corresponding summary statistics.

Data analyses will be conducted using the SAS® System (SAS Institute Inc., Cary, NC). All SAS® programs used to generate analytical results will be developed and validated according to MedImmune SAS® programming standards and MedImmune SAS® validation procedures. Pharmacokinetic analyses will be performed using NONMEM or other appropriate software.

3.2 Subject Populations

Four populations have been defined in this study, the Intention-to-Treat (ITT) Population, the Per-Protocol (PP) Population, the Safety Population, and the Evaluable Population for PK.

3.2.1 Intent-to-treat (ITT) Population

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.

3.2.2 Per-Protocol (PP) Population

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. Major protocol violations include:

- Did not fulfill major eligibility criteria (which will be defined prior to the database lock)
- Developed withdrawal criteria but continued
- Received incorrect investigational treatment/dose

Treatment classification in PP Population will be on 'as-treated' basis.

3.2.3 Safety Population

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.

3.2.4 Evaluable Population for PK

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. Treatment classification in PK Population will be on 'as-treated' basis.

3.3 Baseline Characteristics

Several summaries, which include Subject Population for Evaluation, Number of Subject Randomized by Site, and Status of Randomized Subjects, will be provided to describe the study population. These summaries will aid in interpretation of the assessment of the primary, secondary and exploratory objectives and provide an overview of study conduct.

The summary of the number of subjects randomized by site will be sorted by site number and will contain the primary investigator's name/location.

The summary of randomized subject status at end of study will include an enumeration of the number of subjects who completed the study and the number who did not complete the study due to the following reasons: death, lost to follow-up, withdrawal of consent, and other.

The summary of randomized subject status at end of treatment will include the number of subjects who completed the protocol-defined end of treatment and the number who did not complete due to the following reasons: adverse event, death, lost to follow-up, withdrawal of consent, and other.

All the baseline characteristics (demographics, baseline disease characteristics, medical history and Asthma history) will be summarized by treatment group. In addition demographics and baseline disease characteristics will be summarized by cohort and by treatment group.

The following demographic characteristics will be summarized: age in years, gender, race, ethnicity, weight, height, and Body Mass Index (BMI). BMI is calculated as follows:

$$\text{BMI} = \text{weight (kg)} / [\text{height (m)}]^2$$

The summary of baseline disease characteristics will include descriptive statistics for asthma history, chronic OCS use (presence versus absence), whole blood eosinophil count, atopic asthma status (atopic vs. non-atopic) (Atopy is defined by the presence of elevated IgE specific to any one common aeroallergen on the region-specific ImmunoCap panel tested at baseline), Th2 status identified by serum total IgE and blood eosinophils (Th2-high: IgE >100 IU/mL and blood eosinophils ≥0.14 x 10^9/L) (Corren et al., 2011), serum periostin level, spirometry [pre- and post-bronchodilator FEV_1 and FEV_1 % predicted, FEV_1 reversibility, forced expiratory volume in 6 seconds (FEV_6) and FEV_6 % predicted, FVC, FVC % predicted, FEV1/FVC ratio and inspiratory capacity (IC)], and patient reported outcomes [Asthma Control Questionnaire (6-item version; ACQ-6) score, Asthma Quality of Life Questionnaire Standardized Version (AQLQ(S)), Assessing Symptoms of Moderate-to-severe Asthma (ASMA) Diary, WPAI-Asthma, and EQ-5D] by treatment group.

Prior and concomitant medications will be coded using the latest available version of AstraZeneca Drug Dictionary (AZ DD). All prior and concomitant medications (including those for Asthma indication) will be presented in a data listing.

The compliance with fluticasone/salmeterol maintenance therapy categorized as subjects with ≥ 80% self-reported compliance rate and subjects with < 80% self-reported compliance rate as well as the number and percent of subjects who change their background asthma controller medications post randomization to Week 53 (Stage 1 analysis) and between week 53 and end of study (Stage 2 analysis) will be summarized by treatment group.

Summary	**Population**	**Analysis**
Study Populations for Evaluation		Stage 1
Number of Subjects Randomized by Site	ITT	Stage 1
Status of Randomized Subjects at End of Study	ITT	Stage 2
Status of Randomized Subjects at End of Treatment	ITT	Stage 1
Demographics	ITT	Stage 1
Baseline Disease Characteristics	ITT	Stage 1
Summary of Medical History	ITT	Stage 1
Summary of Asthma History	ITT	Stage 1

Compliance with Fluticasone / Salmeterol Maintenance Therapy	ITT	Stage 1
Number of Subjects with Change of Background Asthma Controller Medications Post Randomization	ITT	Stage 1 / Stage 2

3.4 Study Drug Exposure

The following summary will be provided:

Summary	**Population**	**Analysis**
Number of Study Drug Doses	Safety	Stage 1
Total Amount of Study Drug Exposure in mg	Safety	Stage 1
Total Amount of Study Drug Exposure by Dose in mg/kg	Safety	Stage 1

The summary of study drug exposure will include descriptive statistics for number of study drug doses and total amount of study drug (in both mg and mg/kg) administered to each subject as well as for dose intensity. The total amount of study drug (in mg and mg/kg) administered to the subject is defined as:

Total actual volume administered (ml) × drug concentration (mg/ml) and

Total actual volume administered (ml) × drug concentration (mg/ml) /weight.

For this trial, the drug concentration is 150 mg/ml.

3.5 Summaries to Support the Primary Objective

The primary objective of this study is to evaluate the effect of two SC treatment regimens of 300 mg tralokinumab compared with combined 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. An asthma exacerbation 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 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.

Please note that a single depo-injectable dose of corticosteroid will be considered the equivalent to a 3-day course of systemic corticosteroids

The primary endpoint will be the annual rate of asthma exacerbations experienced by subjects after their first dose of investigational product up to their week 53 / Early Discontinuation visit.

The crude asthma exacerbation rate will be estimated 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 (Pearson Chi-Square correction) with treatment group, age, gender (male vs female), number of asthma exacerbations in the past year (2 vs > 2 but ≤ 6 exacerbations), atopic asthma status (atopic vs. non-atopic), chronic OCS use (presence versus absence), and geographical region (United States/Canada/Western Europe, Eastern Europe, Asia, rest of world) as covariates and the log of number of days in the study as offset. Exacerbation rates, 85% CIs, rate ratios, 2-sided p-values will be provided based on the Poisson regression model. 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.

Severe asthma exacerbations are of interest. The Analyses mentioned above will be conducted specifically for severe asthma exacerbations as well.

In addition, asthma exacerbations and severe asthma exacerbations between week 53 and end of the study, and asthma exacerbations and severe asthma exacerbations through the end of the study will also be summarized. Time to first exacerbation and time to first severe exacerbation will be analyzed as a supportive efficacy analysis to the primary objective. A Cox proportional hazard model will be fitted to data.

The number and proportion of subjects with different number of asthma exacerbations and severe asthma exacerbations (0, 1, 2, 3, and > 3) will be summarized by treatment group.

The following subgroups constitute subgroup populations of interest:

1) Subjects with percentage of predicted FEV1 at baseline ≤ 60%, and ≤ 80%;
2) Subjects with baseline % FEV1 reversibility (>= 12% and < 12%);
3) Subjects with pre-bronchodilator FEV1 improvement at Week 5 and Week 13 (defined as percent change from baseline ≥ 10%) from tralokinumab group;
4) Subjects grouped by number of asthma exacerbations in the past year (2 vs > 2 but ≤ 6 exacerbations);
5) Subject grouped by chronic OCS use (presence vs absence);
6) Subjects grouped by Th2 status (Th2-high: IgE >100 IU/mL and blood eosinophils ≥0.14 x 10^9/L, and Th2-low);
7) Subjects grouped by atopic asthma status (atopic vs. non-atopic);
8) Subjects grouped by baseline serum periostin level (>= median or < median; ; >= 25^{th} percentile vs < 25^{th} percentile; >= 75^{th} percentile vs < 75^{th} percentile);
9) Subjects grouped by baseline peripheral blood eosinophil count (< 150 Cells/UL vs >= 150; < 300 Cells/UL vs >= 300).

The analyses described above except for comparisons between tralokinumab and placebo from the same cohort and for analyses for severe asthma exacerbations will be conducted for these subgroup populations.

For graphic presentation, cumulative number of asthma exacerbations and severe asthma exacerbations over time by treatment group, distribution of number of exacerbation by

treatment group, forest plots of risk ratio (with 85% CI) for asthma exacerbations and severe asthma exacerbations for overall population and for each subgroup, and Kaplan-Meier curve of time to first asthma exacerbation and severe asthma exacerbation by treatment group will be created. Forest plots of risk ratio (with 85% CI) for asthma exacerbations and severe asthma exacerbations will also be created by baseline serum periostin level (< median, and >= Median; >= 25^{th} percentile vs < 25^{th} percentile; >= 75^{th} percentile vs < 75^{th} percentile) and by baseline peripheral blood eosinophil count (< 150 Cells/UL, 150 - < 300, and >= 300).

Summary	**Population**	**Analysis**
Summary of Asthma Exacerbation Rate through Week 53	ITT	Stage 1
Summary of Severe Asthma Exacerbation Rate through Week 53	ITT	Stage 1
Summary of Asthma Exacerbation Rate through Week 53	PP	Stage 1
Summary of Severe Asthma Exacerbation Rate through Week 53	PP	Stage 1
Summary of Asthma Exacerbation Rate between Week 53 and the End of Study	ITT	Stage 2
Summary of Severe Asthma Exacerbation Rate between Week 53 and the End of Study	ITT	Stage 2
Summary of Asthma Exacerbation Rate between Week 53 and the End of Study	PP	Stage 2
Summary of Severe Asthma Exacerbation Rate between Week 53 and the End of Study	PP	Stage 2
Summary of Asthma Exacerbation Rate through the End of Study	ITT	Stage 2
Summary of Severe Asthma Exacerbation Rate through the End of Study	ITT	Stage 2
Summary of Asthma Exacerbation Rate through the End of Study	PP	Stage 2
Summary of Severe Asthma Exacerbation Rate	PP	Stage 2

through the End of Study		
Time-to-First Asthma Exacerbation through Week 53	ITT	Stage 1
Time-to-First Severe Asthma Exacerbation through Week 53	ITT	Stage 1
Time-to-First Asthma Exacerbation through Week 53	PP	Stage 1
Time-to-First Severe Asthma Exacerbation through Week 53	PP	Stage 1
Time-to-First Asthma Exacerbation between Week 53 and the End of Study	ITT	Stage 2
Time-to-First Severe Asthma Exacerbation between Week 53 and the End of Study	ITT	Stage 2
Time-to-First Asthma Exacerbation between Week 53 and the End of Study	PP	Stage 2
Time-to-First Severe Asthma Exacerbation between Week 53 and the End of Study	PP	Stage 2
Time-to-First Asthma Exacerbation through the End of Study	ITT	Stage 2
Time-to-First Severe Asthma Exacerbation through the End of Study	ITT	Stage 2
Time-to-First Asthma Exacerbation through the End of Study	PP	Stage 2
Time-to-First Severe Asthma Exacerbation through the End of Study	PP	Stage 2
Number Subjects with at Least One Asthma Exacerbation through Week 53	ITT	Stage 1
Number Subjects with at Least One Severe Asthma Exacerbation through Week 53	ITT	Stage 1
Number Subjects with at Least One Asthma Exacerbation through Week 53	PP	Stage 1
Number Subjects with at Least One Severe Asthma	PP	Stage 1

Exacerbation through Week 53		
Number Subjects with at Least One Asthma Exacerbation between Week 53 and the End of Study	ITT	Stage 2
Number Subjects with at Least One Severe Asthma Exacerbation between Week 53 and the End of Study	ITT	Stage 2
Number Subjects with at Least One Asthma Exacerbation between Week 53 and the End of Study	PP	Stage 2
Number Subjects with at Least One Severe Asthma Exacerbation between Week 53 and the End of Study	PP	Stage 2
Number Subjects with at Least Asthma Exacerbation through the End of Study	ITT	Stage 2
Number Subjects with at Least Severe Asthma Exacerbation through the End of Study	ITT	Stage 2
Number Subjects with at Least Asthma Exacerbation through the End of Study	PP	Stage 2
Number Subjects with at Least Severe Asthma Exacerbation through the End of Study	PP	Stage 2
Number of Subjects with Different Number of Asthma Exacerbations through Week 53	ITT	Stage 1
Number of Subjects with Different Number of Severe Asthma Exacerbations through Week 53	ITT	Stage 1
Number of Subjects with Different Number of Asthma Exacerbations through Week 53	PP	Stage 1
Number of Subjects with Different Number of Severe Asthma Exacerbations through Week 53	PP	Stage 1

3.6 Summaries to Support the Secondary Objectives

The secondary objectives of this study are:

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 FEV1, FEV6, FVC, FEV1/FVC, IC; and PEF and FEV1 measured at home.
3) To evaluate the effect of tralokinumab on Patient Reported Outcomes: ACQ-6 score, HRQoL using AQLQ[S], and EQ-5D.
4) To evaluate the effect of tralokinumab on asthma symptoms and use of rescue medication using the ASMA diary.
5) To describe the pharmacokinetics (PK) and immunogenicity of tralokinumab.

3.6.1 Safety and Tolerability of Tralokinumab

3.6.1.1 Adverse Events

Adverse events (AE) and serious adverse events (SAE) will be summarized by system organ class, preferred term, severity, and relationship to investigational product. Special information regarding diarrhea and urinary AE is collected through questionnaire in the study. The diarrhea questionnaire and urinary AE questionnaire will be summarized with descriptive statistics.

Injection site reactions are considered an AE of interest for analysis. The Preferred Terms to be included under the definition of "injection site reaction" are outlined in the table below (124 terms). These will be summarized for the overall safety population by cohort and by treatment group.

AE of interest	MedDRA (version 15.1) Preferred Terms
Injection Site Reactions	Administration site abscess, administration site infection, administration site pain, administration site rash, administration site reaction, application site abscess, application site alopecia, application site anaesthesia, application site atrophy, application site burn, application site cellulitis, application site cold feeling, application site dermatitis, application site discharge, application site discolouration, application site discomfort, application site dryness, application site eczema, application site erosion, application site erythema, application site exfoliation, application site fissure, application site folliculitis, application site

	haematoma, application site haemorrhage, application site hyperaesthesia, application site hypersensitivity, application site induration, application site infection, application site inflammation, application site irritation, application site mass, application site necrosis, application site nodule, application site odour, application site oedema, application site pain, application site pallor, application site papules, application site paraesthesia, application site perspiration, application site photosensitivity reaction, application site pruritus, application site pustules, application site rash, application site reaction, application site scab, application site scar, application site swelling, application site telangiectasia, application site ulcer, application site urticaria, application site warmth, application site vesicles, injection site abscess, injection site abscess sterile, injection site anaesthesia, injection site atrophy, injection site calcification, injection site cellulitis, injection site coldness, injection site cyst, injection site dermatitis, injection site discharge, injection site discolouration, injection site discomfort, injection site dryness, injection site dysaesthesia, injection site eczema, injection site erosion, injection site erythema, injection site exfoliation, injection site extravasation, injection site fibrosis, injection site granuloma, injection site haematoma, injection site haemorrhage, injection site hypersensitivity, injection site hypertrophy, injection site induration, injection site infection, injection site inflammation, injection site injury, injection site irritation, injection site ischaemia, injection site laceration, injection site lymphadenopathy, injection site macule, injection site mass, injection site movement impairment, injection site necrosis, injection site nerve damage, injection site nodule, injection site oedema, injection site pain, injection site pallor, injection site papule, injection site paraesthesia, injection site phlebitis, injection site photosensitivity reaction, injection site pruritus, injection site pustule, injection site rash, injection site reaction, injection site recall reaction, injection site scab, injection site scar, injection site streaking, injection site swelling, injection site

	thrombosis, injection site ulcer, injection site urticaria, injection site warmth, injection site vasculitis, injection site vesicles, malabsorption from injection site, puncture site abscess, puncture site discharge, puncture site haemorrhage, puncture site induration, puncture site infection, puncture site pain, puncture site reaction, puncture site swelling

Adverse events may be treatment emergent (i.e., 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.

Adverse event that do not have a valid onset date and where it cannot be ascertained whether the onset date is on or after the first dosing date will be counted as treatment emergent AE (TEAE) and will be included in AE summary tables.

1. For AE with valid onset year and month but missing onset day, (1) if the year of onset date is greater than the year of first dosing date, then the AE is TEAE; (2) if the year of onset is equal to the year of first dosing and the month of the onset is greater than the first dosing date, then the AE is TEAE; (3) if the year and month of onset are equal to the year and month of first dosing date and (the AE stop date is after the date of first dosing date or AE stop date is missing or continuing), then the AE is TEAE.
2. For AE with valid onset year but missing onset month and day, (1) if the year of onset is greater than or equal to the year of first dosing date, then the AE is TEAE; (3) if the year of onset is equal to the year of first dosing date and (the AE stop date is after the first drug dosing or AE stop date is missing or continuing), then the AE is TEAE.
3. For AE with completely missing onset date, if the AE stop date is less than the date of first dosing, then the AE is non-emergent AE; otherwise, count it as TEAE.

Summary	**Population**	**Analysis**
Number of Subjects with Non-Treatment Emergent Adverse Events	Safety	Stage 2
Rate Summary of Non-Treatment Emergent Adverse Events	Safety	Stage 2

Number of Subjects with Treatment Emergent Adverse Events	Safety	Stage 1; Stage 2
Rate Summary of All Treatment Emergent Adverse Events	Safety	Stage 2
Number of Subjects with Treatment Emergent Adverse Events by Highest Severity	Safety	Stage 1; Stage 2
Number of Subjects with Treatment Emergent Adverse Events Sorted by Frequency	Safety	Stage 1; Stage 2
Number of Subjects with Related Treatment Emergent Adverse Events	Safety	Stage 1; Stage 2
Number of Subjects with Related Treatment Emergent Adverse Events by Highest Severity	Safety	Stage 1; Stage 2
Number of Subjects with Non-Treatment Emergent Serious Adverse Events	Safety	Stage 2
Number of Subjects with Treatment Emergent Serious Adverse Events	Safety	Stage 1; Stage 2
Number of Subjects with Treatment Emergent Serious Adverse Events by SAE Criteria	Safety	Stage 1; Stage 2
Number of Subjects with Related Treatment Emergent Serious Adverse Events	Safety	Stage 1; Stage 2
Number of Subjects with Treatment Emergent Serious Adverse Events by Highest Severity	Safety	Stage 1; Stage 2
Non-Treatment Emergent Adverse Events Resulting in Death	Safety	Stage 1; Stage 2
Treatment Emergent Adverse Events Resulting in Death	Safety	Stage 1; Stage 2
Number of Subjects with Treatment Emergent Adverse Events Resulting in Permanent Discontinuation of Study Drug	Safety	Stage 1; Stage 2
Summary of Diarrhea Questionnaire	Safety	Stage 1; Stage 2

Summary of Urinary AE Questionnaire	Safety	Stage 1; Stage 2
Summary of Injection Site AEs	Safety	Stage 1; Stage 2

3.6.1.2 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.

Laboratory measurements will be evaluated with descriptive statistics (N, mean, median, and standard deviation, minimum and maximum) for lab results and changes from baseline at each collection time point. All laboratory values will be included in the listings and values outside of the normal range will be flagged. Shift tables will be provided for Lab result. For laboratory values reported as lower than the limit of quantification (LLOQ), a value equal to half of the limit of quantification will be imputed in the summaries. However, all laboratory measurements will be included in the data listings as reported without any imputation.

The number and percent of patients with blood eosinophil counts >1500 cells/UL will be summarized by treatment group and by visit.

For presentation, change from baseline in blood eosinophil counts over time by treatment group will be plotted for both ITT population and PP population. Intra-patient variability for blood eosinophils will be evaluated during the run-in period (between Week -2 and Week 1 visits).

Summary	**Population**	**Analysis**
Hematology Results	Safety	Stage 1; Stage 2
Serum Chemistry Results	Safety	Stage 1; Stage 2
Change from Baseline in Hematology Results	Safety	Stage 1; Stage 2
Change from Baseline in Serum Chemistry Results	Safety	Stage 1; Stage 2

Shift Table for Hematology	Safety	Stage 1; Stage 2
Shift Table for Serum Chemistry	Safety	Stage 1; Stage 2
Number of Subjects with Blood Eosinophil Counts >1500 cells/UL	Safety	Stage 1; Stage 2
Intra-patient Variability for Blood Eosinophil Counts During the Run-in Period		Stage 1

3.6.1.3 Vital sign

Vital sign (blood pressure, temperature, pulse rate, and respiration rate) results and shift table for vital sign results will be summarized using descriptive statistics. In addition, listing of vital signs will be generated.

Summary	**Population**	**Analysis**
Vital Sign Results	Safety	Stage 1; Stage 2
Shift Table for Vital Sign Results	Safety	Stage 1; Stage 2

3.6.1.4 ECG

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.

The number of subjects with ECG results and the shift table for ECG results will be produced. In addition, the observed values for quantitative assessments (heart rate, PR, QRS, QT, and QTc intervals) and the change from baseline for QT and QTc intervals will be summarized with descriptive statistics. All ECG results will be presented in the data listing.

Summary	**Population**	**Analysis**
Number of Subjects With ECG Results	Safety	Stage 1; Stage 2

Shift Table for ECG Results	Safety	Stage 1; Stage 2
Summary of Quantitative ECG Results	Safety	Stage 1; Stage 2
Change from Baseline in Quantitative ECG Results	Safety	Stage 1; Stage 2

3.6.1.5 Physical Examination

All abnormal physical exam findings (pre and post-dose assessments) will be listed.

3.6.2 The Effect of Tralokinumab on Pulmonary Function

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. The following values will be captured: pre- and post-bronchodilator FEV_1, FEV_6, FVC, FEV_1/FVC, and IC.

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. For the analyses of FEV_6, the highest value will be used. For FEV_1/FVC calculation, the highest FVC and the highest FEV_1 will be selected.

Reversibility is calculated based on the maximum pre- and post-bronchodilator FEV_1 as follows:

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

Spirometry measurements and reversibility as well as the changes from baseline and percent change from baseline will be summarized with descriptive statistics. ANCOVA may be used to compare the change from baseline with age, gender, number of exacerbations in past year

(2 vs > 2 but ≤ 6), atopic asthma status (absence/presence), chronic OCS use (presence versus absence) and geographical region as the potential covariates at Week 53 and Week 75

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.

The weekly morning and evening average of FEV_1 and PEF at home will be summarized by week. The weekly average along with change from baseline and percent change from baseline at various time points will be summarized using descriptive statistics. Diurnal PEF variability defined as 100% x (PM PEF - AM PEF)/((AM PEF +PM PEF)/2), i.e. amplitude % mean will be summarized by visit using descriptive statistics also.

Spirometry data will be summarized for the following subgroups:

1) Subjects with percentage of predicted FEV1 at baseline ≤ 60%, and ≤ 80%;
2) Subjects with baseline % FEV1 reversibility (>= 12% and < 12%);
3) Subjects with pre-bronchodilator FEV1 improvement at Week 5 and Week 13 (defined as percent change from baseline ≥ 10%) from tralokinumab group;
4) Subjects grouped by number of asthma exacerbations in the past year (2 vs > 2 but ≤ 6 exacerbations);
5) Subject grouped by chronic OCS use (presence vs absence);
6) Subjects grouped by Th2 status (Th2-high vs Th2-low);
7) Subjects grouped by atopic asthma status (atopic vs. non-atopic);
8) Subjects grouped by baseline serum periostin level (>= median or < median; >= 25^{th} percentile vs < 25^{th} percentile; >= 75^{th} percentile vs < 75^{th} percentile);
9) Subjects grouped by baseline peripheral blood eosinophil count (< 150 Cells/UL vs >= 150; < 300 Cells/UL vs >= 300).

Unacceptable spirometry data based on "Valid Best Test Review Result" will be excluded from the above analyses.

Absolute measurement over time, change from baseline over time, and percent change from baseline over time by treatment group will be graphed for the following spirometry measurement for overall and subgroups and for ITT population and PP population: pre- and post-bronchodilator FEV_1 (L) and pre-bronchodilator FVC (L).

Summary	**Population**	**Analysis**
Summary of Spirometry Results	ITT	Stage 1; Stage 2

Change from Baseline in Spirometry Results	ITT	Stage 1; Stage 2
Percent Change from Baseline in Spirometry Results	ITT	Stage 1; Stage 2
Summary of Home Peak Flow Testing	ITT	Stage 1; Stage 2
Change from Baseline in Home Peak Flow Testing	ITT	Stage 1; Stage 2
Percent Change from Baseline in Home Peak Flow Testing	ITT	Stage 1; Stage 2
Summary of Change from Baseline in Spirometry Results at Week 53	ITT	Stage 1
Summary of Change from Baseline in Spirometry Results at Week 75	ITT	Stage 2
Summary of Spirometry Results	PP	Stage 1; Stage 2
Change from Baseline in Spirometry Results	PP	Stage 1; Stage 2
Percent Change from Baseline in Spirometry Results	PP	Stage 1; Stage 2
Summary of Home Peak Flow Testing	PP	Stage 1; Stage 2
Change from Baseline in Home Peak Flow Testing	PP	Stage 1; Stage 2
Percent Change from Baseline in Home Peak Flow Testing	PP	Stage 1; Stage 2
Summary of Change from Baseline in Spirometry Results at Week 53	PP	Stage 1
Summary of Change from Baseline in Spirometry Results at Week 75	PP	Stage 2

3.6.3 The Effect of Tralokinumab on Patient Reported Outcomes

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). ACQ-6 will be completed weekly by using an ePRO device. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is computed as the mean of the responses from all 6 items in the questionnaire. Mean ACQ-6 score≤ 0.75 indicates well-controlled asthma, scores greater than

0.75 and less than 1.5 indicates 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).

We intend to follow the guidelines established by Juniper (Elizabeth Juniper, Asthma Control Questionnaire -- Background Administration and Analysis, 2004, QoL Technologies). In order to be more specific, the exact algorithm that will be implemented in imputation of the missing data will be specified in the SPP. The mean ACQ-6 score along with the changes from baseline will be summarized using descriptive statistics. The proportions of subjects achieving mean ACQ-6 ≤ 0.75 (well-controlled), 0.75< mean ACQ-6<1.5 (partly controlled), and mean ACQ-6 of ≥ 1.5 at Week 53 and Week 75 will be evaluated using Fisher's exact test.

The AQLQ(S) is a 32-item questionnaire that measures the health related quality of life experienced by asthma patients (Juniper et al, 1999). 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. The minimal important difference (MID) for the AQLQ(S) total and domain scores is 0.5 (Juniper et al, 1994).

The overall and 4 domain scores from the AQLQ(S) responses along with their respective changes from baseline will be summarized using descriptive statistics by treatment group. Additionally, within each treatment group, the overall and 4 domain scores will be summarized by three categories, improvement (change in scores from baseline ≥ 0.5), no change (-0.5 ≤ change in score from baseline < 0.5), and worse (change in score < -0.5).

Mean ACQ-6 score over time and change from baseline in mean ACQ-6, overall AQLQ(s) score over time and change from baseline in AQLQ(s) over time will be plotted for overall and subgroups (see below) and for ITT population and PP population.

Subgroup analyses on ACQ-6 and AQLQ(s) will be conducted for the following subgroups:

1) Subjects with percentage of predicted FEV1 at baseline ≤ 60%, and ≤ 80%;
2) Subjects with baseline % FEV1 reversibility (>= 12% and < 12%);

3) Subjects with FEV1 improvement at Week 5 and Week 13 (defined as percent change from baseline ≥ 10%) from tralokinumab group;
4) Subjects grouped by number of asthma exacerbations in the past year (2 vs > 2 but ≤ 6 exacerbations);
5) Subjects grouped by chronic OCS use (presence vs absence);
6) Subjects grouped by Th2 status (Th2-high and Th2-low);
7) Subjects grouped by atopic asthma status (atopic vs. non-atopic);
8) Subjects by serum baseline periostin level (>= median or < median; >= 25th percentile vs < 25th percentile; >= 75th percentile vs < 75th percentile);
9) Subjects grouped by baseline peripheral blood eosinophil count (< 150 Cells/UL vs >= 150; < 300 Cells/UL vs >= 300)

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 (EQ VAS), where the subjects are asked to rate their current health on a scale of 0-100, with 0 being the worst imaginable health state. The frequency and the proportion of subjects for each response level for each dimension will be reported by treatment group and by visit. The EQ VAS data will be summarized with descriptive statistics.

The ASMA Diary is a self-completed PRO instrument designed for once daily data capture using an electronic device (e-diary). The diary was developed by MedImmune and UBC to evaluate outcomes in patients aged 12 years and above with inadequately controlled moderate to severe persistent asthma. Each morning 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.

There are three symptom questions in the ASMA diary: daytime frequency (question 1), daytime severity (question 2) and nighttime severity (question 6). All symptom questions are scored from zero to four, where a higher score indicates greater frequency or severity. Asthma symptom scores will be summarized weekly for subjects with at least 4 non-missing records each week. The baseline score should be calculated from day -7 to day -1. Change

from baseline tables will be assessed using descriptive statistics and created for daytime frequency, daytime severity, nighttime severity and overall symptoms ((daytime severity score + daytime frequency score + nighttime severity score)/3). Additionally, proportion of symptom-free days will be calculated (questions 1, 2, 5 and 6 = 0) and presented at weekly intervals from Week -4 until Week 75.

Scores for nighttime awakenings will be generated based on the single item (question 5) which has a dichotomous response option (YES/NO). Nighttime awakening will be summarized weekly for subjects with at least 4 non-missing records each week. The baseline score should be calculated with data from day -7 to day -1. Change from baseline tables will be assessed using descriptive statistics and created for the average number of awakenings per week.

Rescue medication use is collected from three questions: daytime use in response to symptoms (question 3), daytime prophylactic use (question 4) and nighttime use (question 7). Rescue medication use questions are first assessed using a dichotomous response option (YES/NO). If the subject reports YES, there is a subsequent question about the number of times rescue medication was used (questions 3a, 4a and 7a). Daily average scores should be summarized each week for all subjects with at least 4 non-missing records each week. Days with no reported rescue medication use should be represented as zero and included in the calculation with subjects that reported yes and completed questions 3a, 4a and 7a. The baseline score should be calculated from day -7 to day -1. Change from baseline tables will be created for daytime in response to symptoms, nighttime, prophylactic, total without prophylactic and total with prophylactic. Additionally, days without rescue medication use will be calculated (questions 3 and 7 = 0) and presented at weekly intervals from Week -4 until Week 75.

There are three activity limitation questions in the ASMA diary. All activity questions are scored from zero to four, where the higher score indicates greater limitation. Activity limitation scores will be summarized weekly for subjects with at least 4 non-missing records each week. The baseline score should be calculated from day -7 to day -1. Change from baseline tables will be assessed using descriptive statistics and created for overall activity limitation, avoiding activities and pacing during activities.

Summary	**Population**	**Analysis**
Summary of Mean ACQ-6 Scores	ITT	Stage 1; Stage 2

Change from Baseline in Mean ACQ-6 Scores	ITT	Stage 1; Stage 2
Summary of Proportion of Subjects Achieving Mean ACQ-6≤ 0.75, 0.75<Mean ACQ-6<1.5, Mean ACQ-6≥1.5 at Week 53	ITT	Stage 1
Summary of Proportion of Subjects Achieving Mean ACQ-6≤ 0.75, 0.75<Mean ACQ-6<1.5, Mean ACQ-6≥1.5 at Week 75	ITT	Stage 2
Summary of AQLQ(S) Total and Domain Scores	ITT	Stage 1; Stage 2
Change from Baseline in AQLQ(S) Total and Domain Scores	ITT	Stage 1; Stage 2
Summary of AQLQ(S) Response (Improvement, No Change, and Worse)	ITT	Stage 1; Stage 2
Summary of EQ-5D Response	ITT	Stage 1; Stage 2
Change from Baseline in EQ-5D Response	ITT	Stage 1; Stage 2
Summary of EQ VAS Data	ITT	Stage 1; Stage 2
Change from Baseline in EQ VAS Data	ITT	Stage 1; Stage 2
Summary of EQ-5D Index	ITT	Stage 1; Stage 2
Change from Baseline in EQ-5D Index	ITT	Stage 1; Stage 2
Weekly Summary of ASMA Diary: Asthma Symptoms	ITT	Stage 1; Stage 2
Weekly Summary of ASMA Diary: Rescue Medication Use	ITT	Stage 1; Stage 2
Weekly Summary of ASMA Diary: Nighttime awakenings	ITT	Stage 1; Stage 2
Weekly Summary of ASMA Diary: Activity Limitation Scores	ITT	Stage 1; Stage 2
Change from Baseline in ASMA Diary: Asthma Symptoms	ITT	Stage 1; Stage 2

Change from Baseline in ASMA Diary: Rescue Medication Use	ITT	Stage 1; Stage 2
Change from Baseline in ASMA Diary: Nighttime Awakenings	ITT	Stage 1; Stage 2
Change from Baseline in ASMA Diary: Activity Limitation Scores	ITT	Stage 1; Stage 2
Summary of Mean ACQ-6 Scores	PP	Stage 1; Stage 2
Change from Baseline in Mean ACQ-6 Scores	PP	Stage 1; Stage 2
Summary of Proportion of Subjects Achieving Mean ACQ-6≤ 0.75, 0.75<Mean ACQ-6<1.5, Mean ACQ-6≥1.5 at Week 75	PP	Stage 2
Summary of AQLQ(S) Total and Domain Scores	PP	Stage 1; Stage 2
Change from Baseline in AQLQ(S) Total and Domain Scores	PP	Stage 1; Stage 2
Summary of AQLQ(S) Response (Improvement, No Change, and Worse)	PP	Stage 1; Stage 2
Summary of EQ-5D Response	PP	Stage 1; Stage 2
Change from Baseline in EQ-5D Response	PP	Stage 1; Stage 2
Summary of EQ VAS Data	PP	Stage 1; Stage 2
Change from Baseline in EQ VAS Data	PP	Stage 1; Stage 2
Summary of EQ-5D Index	PP	Stage 1; Stage 2
Change from Baseline in EQ-5D Index	PP	Stage 1; Stage 2
Weekly Summary of ASMA Diary: Asthma Symptoms	PP	Stage 1; Stage 2
Weekly Summary of ASMA Diary: Rescue Medication Use	PP	Stage 1; Stage 2
Weekly Summary of ASMA Diary: Activity Limitation Scores	PP	Stage 1; Stage 2

Change from Baseline in ASMA Diary: Nighttime Awakenings	PP	Stage 1; Stage 2
Change from Baseline in ASMA Diary: Activity Limitation Scores	PP	Stage 1; Stage 2

3.6.4 The Pharmacokinetics (PK) and Immunogenicity of Tralokinumab

The PK and IM data of CAT-354 will be evaluated. Individual CAT-354 serum concentrations will be tabulated by treatment group with descriptive statistics. The BLQ observations will be changed to zero for mean concentration calculation. However if the calculated mean is less than the assay LLOQ, the mean value will be set to BLQ according to MedImmune SOP. Missing PK observations will be excluded from the mean calculation and PK data analysis. Anti-drug antibodies (ADA) will be assessed at Week 1, Week 37, Week 59, and Week 75. All valid assay results from subjects who receive any study drug will be included in ADA summaries. All subjects with titer information will be shown in the data listing. A summary of the actual ADA titers by treatment group and visit will also be provided. Study discontinuation blood samples will be summarized at the closest nominal time point that does not already have a value. The association of ADA titers with AEs, PK, and exacerbation rate and other clinical measures will be evaluated.

The PK data will be analyzed and reported separately by MedImmune Global PK-PD & Bioanalysis group.

Summary	**Population**	**Analysis**
Summary of CAT-354 Serum Concentration	PK	Stage 1; Stage 2
Summary of Subjects with Anti-CAT-354 Antibody	PK	Stage 1; Stage 2

3.7 Summaries to Support the Exploratory Objectives

The exploratory objectives of this study are:

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 deoxyribonucleic acid (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.

Healthcare resource utilization will be evaluated by the number and proportion of subjects who were hospitalized due to asthma as recorded on the patient ediary. In addition, descriptive statistics will be provided for number of phone calls with healthcare providers, number of physician office visits, and number of urgent care or emergency department visit.

The WPAI-Asthma is a 6-item questionnaire that assesses productivity and activity impairment over the previous week. There are a maximum of six questions and a minimum of two questions that will be completed by subjects:

1 = currently employment status

2 = hours missed due to health problems

3 = hours missed other reasons

4 = hours actually worked

5 = degree health affected productivity while working

6 = degree health affected regular activities

If the answer to question 1 is yes, currently employed, then the subject should complete all 6 questions. If the answer to question 1 is no, not currently employed, then the subject should only complete questions 1 and 6.

The WPAI-Asthma provides employment status as well as four types of scores: absenteeism (work time missed), presenteeism (impairment at work / reduced on-the-job effectiveness), work productivity loss (overall work impairment / absenteeism plus presenteeism), and activity impairment. WPAI-Asthma outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

Employment status, Question 1, should be summarized as Yes - continuous, Yes – not continuous (Yes response to some weeks during the study), and No for each treatment group and representing the data between Weeks 3-53.

Questions 2-4 should be summarized cumulatively between weeks 3-53 for each treatment group and stratified by employment status. Questions 5-6 should be summarized as the average between weeks 3-53 for each treatment group for all subjects and stratified by employment status.

The following calculations should be used to create the outcomes of interest:

Absenteeism = Q2/(Q2+Q4)

Presenteeism = Q5/10

Work Productivity Loss = Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)]

Activity Impairment = Q6/10

The effect of tralokinumab on airway wall thickening using high-resolution computed tomography will be analyzed separately and a separate statistical analysis plan will be prepared.

For serum proteins, change from baseline and percentage change from baseline will be summarized by treatment group and by baseline periostin level (high vs low, in which high is defined as ≥ median value and low defined as < median value). For mRNA, we will compare gene expression profiles between responders and non-responders to tralokinumab using multivariate approaches including clustering.

Total IgE measurements, changes from baseline in total IgE, and percent changes from baseline in total IgE will be summarized with descriptive statistics (N, mean, median, standard deviation, minimum and maximum) at each collection time point.

Intra-patient variability for serum periostin will be evaluated during the run-in period (between Week -2 and Week 1 visits). Serum periostin over time, change from baseline, and percent change from baseline will be summarized by treatment group.

For presentation, percent change from baseline in total IgE and periostin over time by treatment group will be plotted for both ITT population and PP population.

Summary	**Population**	**Analysis**
Summary of Health Resource Utilization Data	ITT	Stage 1
Summary of Health Resource Utilization Data	PP	Stage 1
Summary of WPAI-Asthma Data	ITT	Stage 1
Summary of WPAI-Asthma Data	PP	Stage 1

Summary of Periostin Results	ITT	Stage 1; Stage 2
Change from Baseline in Periostin Results	ITT	Stage 1; Stage 2
Percent Change from Baseline in Periostin Results	ITT	Stage 1; Stage 2
Summary of Periostin Results	PP	Stage 1; Stage 2
Change from Baseline in Periostin Results	PP	Stage 1; Stage 2
Percent Change from Baseline in Periostin Results	PP	Stage 1; Stage 2
Summary of Total IgE Results	ITT	Stage 1; Stage 2
Change from Baseline in Total IgE Results	ITT	Stage 1; Stage 2
Percent Change from Baseline in Total IgE Results	ITT	Stage 1; Stage 2
Summary of Total IgE Results	PP	Stage 1; Stage 2
Change from Baseline in Total IgE Results	PP	Stage 1; Stage 2
Percent Change from Baseline in Total IgE Results	PP	Stage 1; Stage 2
Intra-patient Variability for Serum Periostin During the Run-in Period		Stage 1

4 Missing Data

Missing data will not be imputed unless otherwise specified.

5 General Statistical Conventions

- Laboratory data reported as ND (not done) will be counted as missing when calculating summary statistics.
- In general, all calculations will be performed prior to rounding.
- All percentages will be formatted as (xx.x%) with the exception of 100% which will be displayed as (100%). For 100% and percentages less than 10, a space will be included between the "(" and the first digit, for example, (6.3%) rather than (6.3%). For 0%, the percentage will be displayed as (0.0%).

- P-values will be rounded to three decimal digits. P-values that are less than 0.001 will be reported as "< 0.001" on the tables.
- For analyses of pre-dose laboratory data, if the time of the pre-dose laboratory collection actually occurs after dosing, the data will be excluded from analyses.
- If N = 1, then the standard deviation and/or standard error should be displayed as "NA". If N= 0, then all summary statistics (other than N) will be displayed as "NA".

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