A Phase 1 Study to Evaluate the Pharmacokinetics and Tolerability of a Single Subcutaneous Dose of Tralokinumab When Delivered as a 2 mL Injection at Different Flow Rates to Healthy Volunteers

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PROTOCOL SYNOPSIS

TITLE

A Phase 1 Study to Evaluate the Pharmacokinetics and Tolerability of a Single Subcutaneous Dose of Tralokinumab When Delivered as a 2 mL Injection at Different Flow Rates to Healthy Volunteers

HYPOTHESES

Primary Hypothesis: The primary hypothesis to be tested is that delivery of a single 2 mL subcutaneous (SC) injection of 300 mg tralokinumab at different flow rates has no significant impact on its pharmacokinetic (PK) profile as compared to delivery as 2 × 1 mL injections.

Secondary Hypotheses

1. Increasing the volume of injection of tralokinumab from 1 mL to 2 mL reduces the tolerability of the injection at a given flow rate (as measured by pain, pruritus, and local injection-site reactions)
2. Decreasing the flow rate of injection of tralokinumab improves the tolerability of the injection (as measured by pain, pruritus, and local injection site reactions)

OBJECTIVES

Primary Objective: To evaluate the PK profile of a single SC dose of 300 mg tralokinumab when delivered as a 2 mL injection at different flow rates to healthy adult volunteers

Secondary Objectives

1. To determine the local tolerability and overall safety profile of a single SC dose of 300 mg tralokinumab when delivered as a 2 mL injection at different flow rates
2. To determine the immunogenicity profile of a single SC dose of 300 mg tralokinumab when delivered as a 2 mL injection at different flow rates

Exploratory Objectives

To determine the effect of a single SC dose of 300 mg tralokinumab when delivered as a single 2 mL injection at different flow rates in healthy volunteers on biomarkers relevant to the mechanism of action of tralokinumab

STUDY ENDPOINTS

Primary Endpoint: The primary endpoint is the PK profile of tralokinumab.

Secondary Endpoints

1. Local injection site pain intensity and injection site pruritus post-injection
2. Local injection site reactions (eg, erythema, bleeding, rash, etc) post-injection
3. Presence of fluid leakage immediately post-injection
4. Incidence of treatment-emergent adverse events including clinically significant changes in vital signs, physical examinations, and laboratory parameters
5. Presence of anti-drug antibodies to tralokinumab

Exploratory Endpoints

Assessment of biomarkers (including periostin and dipeptidyl peptidase-4) relevant to the mechanism of action of tralokinumab

STUDY DESIGN

Wisenfeld-Hallin, 2005; Paller et al, 2009), randomization will be stratified by gender. A minimum of 5 males and 5 females will be randomized to each cohort; the additional subjects may be of either sex. All injections will be administered SC in the abdomen using a syringe pump and SC insertion set at the following flow rates:

- Cohort 1: 2 × 1 mL SC injections, with each injection delivered at a rate of 6 mL/minute (min)

- Cohort 2: 1 × 2 mL SC injection delivered at a rate of 12 mL/min
- Cohort 3: 1 × 2 mL SC injection delivered at a rate of 2 mL/min
- Cohort 4: 1 × 2 mL SC injection delivered at a rate of 0.167 mL/min

A screening visit will be performed within 21 days prior to dosing. Subjects will be admitted to the study unit on Day -1. Following administration of 300 mg tralokinumab on Day 1, subjects will be followed up for 57 days for safety, tolerability, immunogenicity, and PK sampling.

Subjects will be in this study for up to 79 days, which includes a screening/consent period of up to 21 days, a 1-day treatment period, and a 57-day post-treatment follow-up period.

TARGET SUBJECT POPULATION

The study population will be healthy male and female volunteers ages 19-65 years.

INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

A total of 60 subjects (15 subjects each cohort) will be assigned to 1 of 4 cohorts to receive a single dose of 300 mg tralokinumab SC at the following flow rates:

- Cohort 1: 300 mg tralokinumab as 2 × 1 mL SC injections, with each injection administered at a flow rate of 6 mL/min
- Cohort 2: 300 mg tralokinumab as a 1 × 2 mL SC injection administered at a flow rate of 12 mL/min
- Cohort 3: 300 mg tralokinumab as a 1 × 2 mL SC injection administered at a flow rate of 2 mL/min
- Cohort 4: 300 mg tralokinumab as a 1 × 2 mL SC injection administered at a flow rate of 0.167 mL/min

All injections will be administered SC in the abdomen using a syringe pump and SC insertion set.

STATISTICAL ANALYSIS PLAN

Analysis Populations

The PK population is defined as all subjects in the as-treated population with at least one detectable tralokinumab serum concentration and for whom the PK parameters can be adequately estimated.

The as-treated population includes all subjects who receive any amount of investigational product. Subjects will be included in the as-treated population according to the injection flow rate received even if different from that to which the subject was randomized. Demographics, safety and tolerability endpoints, and biomarkers will be summarized based on the as-treated population.

Planned Analysis

Using the serum concentrations of tralokinumab, the PK parameters will be analyzed using noncompartmental models. Given the small sample size and the exploratory nature of the study, mainly descriptive statistics will be provided for the secondary and exploratory endpoints by cohort over time. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by mean, standard deviation, median, and range. The distribution of pain intensity scores will be examined and the between-cohort difference will be explored.

Sample Size/Power Calculation

The number of subjects planned for this study is based on the number required to obtain adequate PK data while exposing as few healthy volunteer subjects as possible to tralokinumab and procedures. A total of 15 subjects per treatment arm is considered sufficient to detect an approximately 1.5-fold difference in PK parameters between cohorts and will provide exploratory information regarding local tolerability.

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
AHR	airway hyper-responsiveness
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the serum concentration-time curve
$AUC_{0-\infty}$	area under the serum concentration-time curve from zero to infinity
AUC_{0-t}	area under the serum concentration-time curve to last observation
BD	Becton, Dickinson, and Company
BP	blood pressure
CAT-354	tralokinumab
CL/F	apparent systemic clearance
C_{max}	maximum concentration
CV	coefficient of variation
DNA	deoxyribonucleic acid
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
eCRF	electronic case report form
FEV_1	forced expiratory volume in one second
FSH	follicle-stimulating hormone
G	gauge
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IgE/G	immunoglobulin E/G
IL-13	interleukin-13
IRB	Institutional Review Board
IV	intravenous
LABA	long-acting β2-agonist
mAb	monoclonal antibody
min	minute(s)

Abbreviation or Specialized Term	Definition
MSRB	MedImmune Safety Review Board
PEF	peak expiratory flow
PK	pharmacokinetic(s)
Q2W	every 2 weeks
Q4W	every 4 weeks
SABA	short-acting β2-agonist
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SID	subject identification
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
Th2	T-helper-2
T_{max}	time to maximum concentration
ULN	upper limit of normal
USA	United States of America
VAS	visual analogue scale
Vz/F	apparent terminal-phase volume of distribution
WBDC	Web Based Data Capture

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, 2012) 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 E (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; Chipps et al, 2012), 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; Barnes et al, 1996; Accordini et al, 2006). 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 including inflammation, airway hyper-responsiveness (AHR), fibrosis, and increased mucous production. Elevated IL-13 levels have been identified in the sputum of a proportion of patients with asthma including those with severe disease treated with systemic corticosteroids (Saha et al, 2008). Therefore, a significant role for IL-13 in asthma can be expected. Coupled with the evidence of a relationship between IL-13 expression and disease severity in patients, neutralization of IL-13 by tralokinumab is a credible approach to the treatment of asthma.

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

1.2 Tralokinumab Background

Tralokinumab is briefly described below. Refer to the current IB for details.

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 receptors. 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 neutralization of IL-13 activity. Tralokinumab resulted from reformatting the precursor as a human IgG4 isotype (CAT-354) by recombinant DNA technology.

1.3 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-observed-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).

1.4 Summary of Clinical Experience

Seven clinical studies have been completed with tralokinumab in asthma and one study is ongoing. These include 5 completed Phase 1 studies (Studies CAT-354-0401, CAT-354-0602, CAT-354-0703, MI-CP224, and CD-RI-CAT-354-1054), 2 completed Phase 2a studies (Studies CAT-354-0603 and MI-CP199), and 1 ongoing Phase 2b study (Study CD-RI-CAT-354-1049).

The largest study completed to date, Study MI-CP199, was a Phase 2a study in which tralokinumab (150, 300, or 600 mg) or placebo was administered as a SC injection every 2 weeks (Q2W) for 3 months to 194 adult patients with uncontrolled, moderate-to-severe, persistent asthma requiring treatment with appropriate asthma controller medication. The results of this study (Piper et al, 2013) demonstrated a clinical effect with the addition of SC tralokinumab to standard asthma controller medications. An increase in pre-bronchodilator forced expiratory volume in one second (FEV_1) was observed at the first scheduled visit (2 weeks) after first dose of tralokinumab. At Day 92 (Week 13), 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 group (150, 300, and 600 mg; $p = 0.072$). Across the majority of study time points, the magnitude of the increase in FEV_1 was similar in the 300 and 600 mg tralokinumab groups, while smaller improvements were observed in the 150 mg tralokinumab group. In addition, increases from baseline in office peak expiratory flow (PEF) and forced vital capacity, and a reduction in the requirement for the use of additional short-acting β2-agonist (SABA) were also observed in this study. Nearly 95% of the patients completed treatment as planned. The majority of treatment-emergent adverse events (TEAEs) were mild or moderate in severity, and there was a higher frequency of severe and serious TEAEs in the placebo group compared to the combined tralokinumab group. The most frequently reported TEAEs (incidence > 5%) in the combined tralokinumab group were asthma, headache, nasopharyngitis, and bacteriuria; the most frequently reported TEAEs (incidence > 5%) in the placebo group were nasopharyngitis, asthma, decreased neutrophil count, decreased lymphocyte count, and bronchitis. In addition, there were no confirmed anti-drug antibodies (ADA) to tralokinumab in any patient.

Study CD-RI-CAT-354-1049 is an ongoing Phase 2b, randomized, double-blind, placebo-controlled, parallel-arm, multicenter study to evaluate the efficacy and safety of two SC treatment regimens of tralokinumab (300 mg as 2 SC injections Q2W for 50 weeks or 300 mg as 2 SC injections Q2W for 12 weeks followed by every 4 weeks [Q4W] for 38 weeks) in adult patients with uncontrolled, severe asthma requiring high-dose ICS and LABA with or without additional controller medications. Recruitment to this study is complete and interim data analysis is ongoing.

In addition to asthma, tralokinumab is also being studied for other indications, including idiopathic pulmonary fibrosis and ulcerative colitis. Further information and a full list of citations can be found in the IB.

1.5 Rationale for Conducting the Study

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 an increase in FEV_1 compared with placebo and an acceptable safety profile; therefore, further study of tralokinumab as a potential therapeutic asthma-controller therapy is warranted.

A target dose of 300 mg tralokinumab administered as 2 × 1 mL SC injections has been established. Development of a device to support large volume delivery of tralokinumab (by large volume bolus injector or large volume autoinjector) is planned to enable the target dose to be delivered by a single injection rather than 2 individual injections. For this to be feasible, the pharmacokinetic (PK) profile of 300 mg tralokinumab when delivered via different regimens (ie, 2 injections versus 1 injection) should be equivalent and injections of the larger injection volumes (2 mL) must be tolerable for the subject. However, some evidence suggests that larger injection volumes may be associated with a higher incidence of injection site reactions, particularly increased pain intensity (Jorgensen et al, 1996). This is likely due to associated increased SC tissue pressure, which in turn may be influenced by the injection flow rate. The relationship between these variables (injection volume, injection flow rate, and local injection site tolerability) for tralokinumab is currently unknown.

The aim of the present study is to evaluate the PK and tolerability of 300 mg tralokinumab when administered SC by a single larger volume injection of 2 mL at different flow rates compared to that observed with the current method of administration (2 × 1 mL injections). The data gathered from this exploratory study is expected to characterize the relationship between injection volume, flow rate, and local injection site tolerability of tralokinumab, and the subsequent effect of changes in injection volume and flow rate on the observed PK for the molecule. This information will be used to optimize the design specifications for the future delivery device and to plan future studies.

The primary hypothesis to be tested is that delivery of a single 2 mL SC injection of 300 mg tralokinumab at different flow rates has no significant effects on its PK profile compared to delivery as 2 × 1 mL injections. Therefore, the effect of the delivery of a single 2 mL SC injection via different flow rates on the observed PK will be primarily evaluated. The tolerability of delivery of a single 2 mL SC injection of 300 mg tralokinumab at different flow rates will be investigated by recording local injection site reactions as well as injection site pain intensity and injection site pruritus.

With respect to safety, in clinical studies completed to date, tralokinumab was adequately tolerated. A number of potential risks have been identified that are described in the current IB and measures are in place in this study to protect participating subjects as follows:

- Close monitoring of subjects during the study
- 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 Studies MI-CP199, no hypersensitivity reactions were reported following repeat SC dosing. As a precautionary measure in this study, subjects will be monitored closely during the post-dosing period. Vital signs will be taken immediately after administration of investigational product and 10, 30, 60 minutes, and 4 and 8 hours thereafter. Discharge will be at the discretion of the investigator. There will be 7 subsequent study site visits in the 21-day period post-injection and a further 2 visits through the end of the Follow-up Period.
- Subjects will be monitored for both clinical manifestations that may be associated with the development of specific antibodies to tralokinumab and for the presence of such antibodies
- 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 from participating in the study
- Subjects with a history of tuberculosis (TB) requiring treatment within the 12 months prior to the screening visit will be excluded from participating in the study
- Subjects with a history of a clinically significant infection requiring antibiotic therapy or antiviral medication from 30 days prior to screening will be excluded from the study

In conclusion, 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 previously identified and to closely monitor each subject. The current risk/benefit ratio is favorable and justifies the administration of tralokinumab for the purposes of achieving the objectives of this study.

1.6 Research Hypotheses

1.6.1 Primary Hypothesis

The primary hypothesis to be tested is that delivery of a single 2 mL SC injection of 300 mg tralokinumab at different flow rates has no significant impact on its PK profile as compared to delivery as 2 × 1 mL injections.

1.6.2 Secondary Hypotheses

The secondary hypotheses to be tested are:

1. Increasing the volume of injection of tralokinumab from 1 mL to 2 mL reduces the tolerability of the injection at a given flow rate (as measured by pain, pruritus, and local injection site reactions)
2. Decreasing the flow rate of injection of tralokinumab improves the tolerability of the injection (as measured by pain, pruritus, and local injection site reactions)

2 OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

To evaluate the PK profile of a single SC dose of 300 mg tralokinumab when delivered as a 2 mL injection at different flow rates to healthy adult volunteers

2.1.2 Secondary Objectives

1. To determine the local tolerability and overall safety profile of a single SC dose of 300 mg tralokinumab when delivered as a 2 mL injection at different flow rates
2. To determine the immunogenicity profile of a single SC dose of 300 mg tralokinumab when delivered as a 2 mL injection at different flow rates

2.1.3 Exploratory Objectives

To determine the effect of a single SC dose of 300 mg tralokinumab when delivered as a single 2 mL injection at different flow rates in healthy volunteers on biomarkers relevant to the mechanism of action of tralokinumab

2.2 Study Endpoints

2.2.1 Primary Endpoint

The primary endpoint is the PK profile of tralokinumab.

2.2.2 Secondary Endpoint(s)

1. Local injection site pain intensity and injection site pruritus post-injection
2. Local injection site reactions (eg, erythema, bleeding, rash, etc) post-injection
3. Presence of fluid leakage immediately post-injection
4. Incidence of TEAEs including clinically significant changes in vital signs, physical examinations, and laboratory parameters

5. Presence of ADA to tralokinumab

2.2.3 Exploratory Endpoint(s)

Assessment of biomarkers (including periostin and dipeptidyl peptidase-4 [DPP-4]) relevant to the mechanism of action of tralokinumab

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This is a Phase 1, open-label, assessor-blind, parallel-group study to evaluate the PK and tolerability of a single SC dose of 300 mg tralokinumab when delivered as a 2 mL injection at different flow rates to healthy adult volunteers. A total of 60 subjects at one site in the [redacted] will be randomized in a 1:1:1:1 ratio to 1 of 4 cohorts to receive a single SC dose of 300 mg tralokinumab. Due to the potential for gender differences in pain perception and sensitivity (Wisenfeld-Hallin, 2005; Paller et al, 2009), randomization will be stratified by gender. A minimum of 5 males and 5 females will be randomized to each cohort; the additional subjects may be of either sex. All injections will be administered SC in the abdomen using a syringe pump and SC insertion set at the following flow rates:

- Cohort 1: 2 × 1 mL SC injections, with each injection administered at a rate of 6 mL/minute (min)
- Cohort 2: 1 × 2 mL SC injection administered at a rate of 12 mL/min
- Cohort 3: 1 × 2 mL SC injection administered at a rate of 2 mL/min
- Cohort 4: 1 × 2 mL SC injection administered at a rate of 0.167 mL/min

A screening visit will be performed within 21 days prior to dosing. Subjects will be admitted to the study unit on Day -1. Following administration of 300 mg tralokinumab on Day 1, subjects will be followed up for 57 days for safety, tolerability, immunogenicity, and PK sampling. A study flow diagram is presented in Figure 3.1.1-1.

Subjects will be in this study for up to 79 days, which includes a screening/consent period of up to 21 days, a 1-day treatment period, and a 57-day post-treatment follow-up period.

The endpoints to be measured in this study are described in Section 2.2.

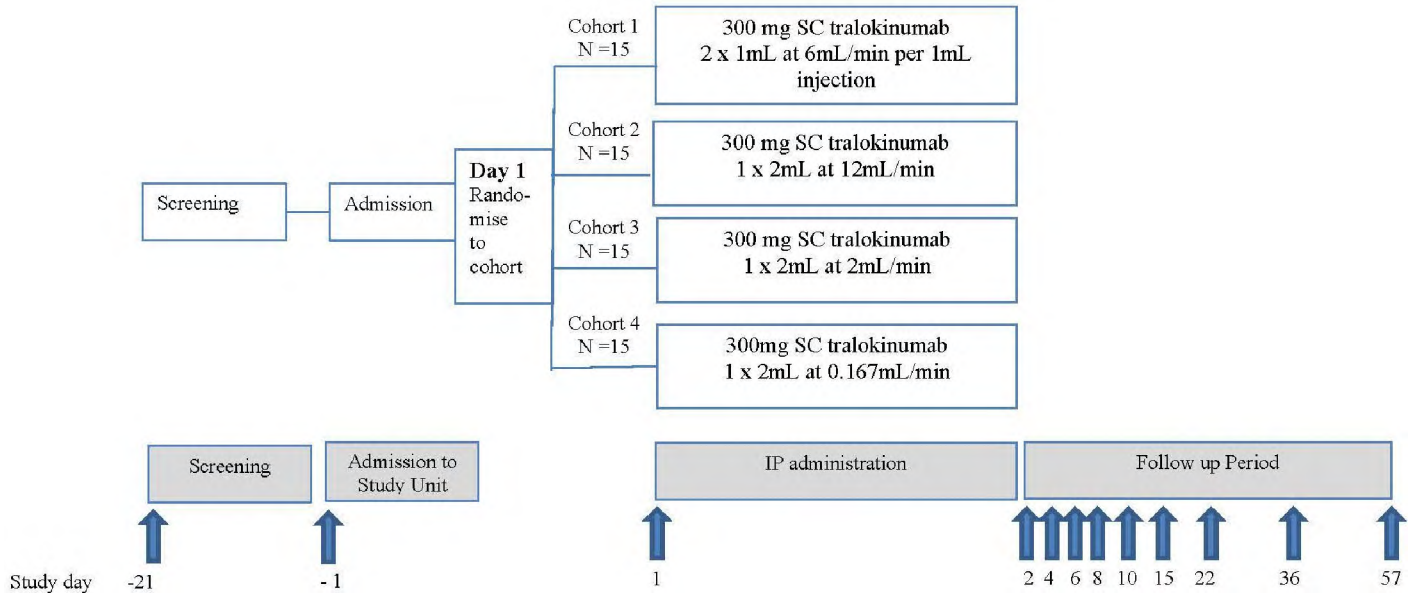

Figure 3.1.1-1 Study Flow Diagram

IP = investigational product; min = minute; N = number of subjects.

3.1.2 Treatment Regimen

A total of 60 subjects will be randomized in a 1:1:1:1 ratio to 1 of 4 cohorts to receive a single SC dose of tralokinumab as described in Table 3.1.2-1. Randomization will be stratified by gender. At a minimum, 5 males and 5 females will be randomized to each cohort; the additional subjects may be of either sex.

Table 3.1.2-1 Investigational Product Dose and Treatment Regimen

Cohort	N	Day 1
1	15	300 mg tralokinumab as 2 × 1 mL SC injections, with each injection administered at a flow rate of 6 mL/min
2	15	300 mg tralokinumab as a 1 × 2 mL SC injection administered at a flow rate of 12 mL/min
3	15	300 mg tralokinumab as a 1 × 2 mL SC injection administered at a flow rate of 2 mL/min
4	15	300 mg tralokinumab as a 1 × 2 mL SC injection administered at a flow rate of 0.167 mL/min

N = number of subjects; SC = subcutaneous.

All injections will be administered into the abdomen via the SC route at the flow rates specified above using a syringe pump and SC insertion set.

3.2 Study Design and Dose Rationale

3.2.1 Dose Rationale

In a previous study in subjects with asthma (Study MI-CP199), treatment with 300 mg tralokinumab Q2W was well-tolerated and showed an effect on FEV_1. Doses lower than 300 mg were found to result in suboptimal increase in FEV_1; therefore, this dose is considered the most appropriate to determine the effect of modulating the dosing administration regimen for the current study. However, tralokinumab is formulated at a concentration of 150 mg/mL and currently requires 2 × 1 mL SC injections to deliver the target dose. Development of an alternative method to support delivery of larger volumes of tralokinumab (via large volume bolus injector or large volume autoinjector) is planned to enable the target dose to be delivered via a single injection rather than 2 separate injections.

3.2.2 Rationale for Study Population

The aim of this study is to evaluate the PK and tolerability of a single SC dose of 300 mg tralokinumab. No efficacy outcomes are planned and the likelihood of clinical benefit for an asthma subject following a single dose of tralokinumab is low based on previous data and modeling predictions. Therefore, healthy adult volunteers have been chosen to aid retention and ensure that the primary study objectives are met. The use of this population is further

supported by data from PK modeling, which has demonstrated that there is no effect of the presence or absence of asthma on the PK profile of tralokinumab, and provides confidence in the applicability of the results.

3.2.3 Rationale for Endpoints

Primary Endpoint

The primary endpoint of the study is the PK of tralokinumab. Each subject will receive a single dose of 300 mg tralokinumab by one of 4 administration regimens and 57 days of follow up. Based on prior data, the maximum concentration $_{(Cmax)}$ of tralokinumab usually occurs between 2-9 days with a half-life of approximately 21 days following SC administration. Therefore, the sampling scheme will provide adequate samples for the characterization of $_{Cmax}$ and area under the serum concentration-time curve (AUC) parameters through noncompartmental analysis. The PK parameters associated with a single 2 mL injection of tralokinumab at different flow rates will be compared to those associated with 2 × 1 mL injections of tralokinumab to determine the feasibility of larger volume delivery and to provide information to aid in the design of the final device.

Secondary Endpoints

Injection site pain will be measured using a 100 mm visual analogue scale (VAS; see Appendix 4). Local injection-site tolerability parameters will also be measured, including injection-site itch and visual assessment of the injection site for reactions such as erythema, rash, etc. As local injection-site reactions are of specific interest, they will be recorded in detail on a dedicated and standardized injection-site questionnaire (Appendix 2) at each time point post-injection. These targeted assessment events will not require reporting as adverse events (AEs) on the AE electronic case report form (eCRF), unless they meet one or more of the following criteria:

- Fulfils the criteria for a serious adverse event (SAE)
- Leads to premature termination of the injection during investigational product administration
- Requires concomitant medication or other medically important intervention
- Has an impact on the general condition of the subject as judged by the investigator

These data will be used to determine the overall tolerability of a single 2 mL injection of tralokinumab at different flow rates to determine the feasibility of this approach compared to 2 × 1 mL injections and to provide information to aid in the design of the final delivery device.

The degree of fluid leakage from the injection site will be assessed immediately following all injections to determine if the flow rates affect delivery of the 2 mL injection volume.

Adverse events and immunogenicity of tralokinumab will also be reported to ensure ongoing monitoring of the safety profile for this investigational product.

Exploratory Endpoints

Serum for assessment of biomarkers relevant to the mechanism of action of tralokinumab, including periostin and DPP-4 levels, will be collected to establish reference values in healthy individuals to compare with prior data collected from subjects with asthma in previous studies and to determine if these levels change following treatment with tralokinumab in this subject group. These data will be analyzed separately by the sponsor.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

A total of 60 subjects will be randomized in a 1:1:1:1 ratio to 1 of 4 cohorts to receive a single SC dose of 300 mg tralokinumab administered as either 2 × 1 mL SC injections at a flow rate of 6 mL/min for each injection (Cohort 1) or a 1 × 2 mL SC injection at flow rates of 12, 2, or 0.167 mL/min (Cohorts 2, 3, or 4, respectively). At minimum, 5 males and 5 females will be randomized to each cohort; the additional subjects may be of either sex.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Healthy males and females ages 19-65 years inclusive at the time of screening
2. Written informed consent and any locally required authorization obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
3. Body mass index of 19.0-30.0 kg/m^2
4. Intact normal skin without potentially obscuring tattoos, scars, pigmentation, or lesions on the abdominal area intended for injection
5. No clinically significant abnormality on the basis of medical/medication history or physical examination
6. Vital signs, electrocardiogram (ECG), and laboratory parameters within normal range, or if outside normal range deemed not clinically significant by the Principal Investigator or medical monitor

7. Negative alcohol and drug screens
8. Able and willing to comply with the requirements of the protocol
9. Females of childbearing potential who are sexually active (ie, do not practice complete abstinence) with a nonsterilized male partner must use highly effective contraception (confirmed by the investigator) from screening, and must agree to continue using such precautions until 3 months after the day of dosing; cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Females must have a negative pregnancy test at the time of screening and prior to randomization for inclusion in the study.
    - Females of childbearing potential are defined as those who are not surgically sterile (ie, have not undergone bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause and follicle-stimulating hormone [FSH] levels consistent with menopausal status).
    - 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 4.1.2-1.
10. Nonsterilized males who are sexually active with a female partner of childbearing potential must use highly effective contraception (see Table 4.1.2-1) from screening until 3 months after the day of dosing; cessation of contraception after this point should be discussed with a responsible physician.

Table 4.1.2-1 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Male condom plus spermicide • Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®) [a]	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

[a] This is also considered a hormonal method.

4.1.3 Exclusion Criteria

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

1. Concurrent enrollment in another clinical study where the subject is receiving an investigational product
2. Individuals who are legally institutionalized
3. Receipt of any marketed or investigational biologic agent within 4 months or 5 half-lives prior to screening, whichever is longer
4. Receipt of any investigational nonbiologic agent within 3 months or 5 half-lives prior to screening, whichever is longer

5. Known history of allergy or reaction to any component of the investigational product formulation
6. History of anaphylaxis following any biologic therapy
7. Current use of regular pain-modifying, anti-depressant, anxiolytic, or hypnotic medication
8. History of thrombocytopenia or bleeding disorder or use of anticoagulants such as warfarin, heparin/low molecular weight heparin, thrombin inhibitors (dabigatran and others), or factor Xa inhibitors (rivaroxaban, apixaban, and others)
9. Any pathology on abdomen that could potentially interfere with study outcome or interpretation of results
10. History of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator
11. Pregnant or breastfeeding women
12. Any active medical or psychiatric condition or other reason 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
13. Any clinically relevant abnormal findings in physical examination, ECG, vital signs, hematology, clinical chemistry, or urinalysis during screening, 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
14. History of any known immunodeficiency disorder or use of immunosuppressive medication
15. History of a clinically significant infection requiring antibiotics or antiviral medication from 30 days prior to screening, up to and including Day 1
16. Diagnosis of a helminth parasitic infection within 6 months prior to screening that has not been treated with, or has failed to respond to, standard of care therapy
17. 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
18. Tuberculosis requiring treatment within the 12 months prior to the screening visit
19. 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 enroll.
20. 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
21. Evidence of active liver disease, including jaundice or aspartate transaminase (AST), alanine transaminase (ALT), or alkaline phosphatase greater than twice the upper limit of normal (ULN)
22. Major surgery within 8 weeks prior to Visit 1, or planned in-patient surgery or hospitalization during the study period

23. Receipt of live attenuated vaccines 30 days prior to screening, up to and including Day 1

4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is “enrolled”) once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned and the screening evaluations may 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 and/or are not randomized), including the reason(s) for screening failure.

If at the screening visit, a subject provides a medical history that is exclusionary but the subject is expected to subsequently become eligible (eg, fails a time-sensitive exclusion criterion), one repeat screening visit will be permitted. Such subjects will receive the same SID number that they were originally assigned.

4.1.5 Withdrawal from the Study

Subjects are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.6 Replacement of Subjects

Subjects who do not receive tralokinumab after being randomized or do not complete the required evaluations through Day 8 will be replaced to maintain the stipulated number of subjects in each cohort (N = 15). Replacement subjects will receive the same treatment assignment as the subject being replaced and every attempt will be made to ensure that they are from the same gender group. Subjects who do not complete the required evaluations beyond Day 8 will not be replaced.

4.1.7 Withdrawal of Informed Consent for Data and Biological Samples

Biological Samples Obtained for the Main Study

Study data are protected by the use of an SID 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 samples 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.

4.2 Schedule of Study Procedures

4.2.1 Enrollment/Screening Period

Table 4.2.1-1 shows all procedures to be conducted at the screening visit. Screening evaluations may be conducted over more than one visit; however, the results of all laboratory tests must be available prior to dosing on Day 1.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and then blood draws.

Table 4.2.1-1 Schedule of Screening Procedures

Study Period	Consent/Screening
Visit Number	**V1**
Procedure / Study Day or Week	**Day -21 to Day -1**
Written informed consent/assigmnent of SID number	X
Verify eligibility criteria	X
Demography and medical history	X
Physical examination, height, and weight	X
12-lead ECG	X
Assessment of AEs/SAEs	X
Concomitant medications	X
Vital signs	X
Blood collection for:	X
Serum chemistry and hematology	X
Pregnancy test (serum (3HCG)	X
Virology: HBsAG, HCAb; HIV-1, HIV-2	X
Urine collection for:	X
Urinalysis	X
Urine drug screen	X

AE = adverse event; PHCG = beta-human chorionic gonadotrop in; ECG = electrocardiogram; HBsAG = hepatitis B surface antigen; HCAb = hepatitis C antibody; HIV = human inummodeficiency virus; SAE = serious adverse event; SID = subject identification; V = visit.

4.2.2 Treatment Period

Table 4.2.2-1 shows all procedures to be conducted during the treatment period.

Table 4.2.2-2 shows the timing of Day 1 assessments in more detail.

Table 4.2.2-1 Schedule of Treatment Procedures

Study Period	Admission to Study Unit	Treatment
Visit Number	**V2**	**V2**
Procedure / Study Day or Week	**Day -1**	**Day 1**
Verify eligibility criteria	X	X[a]
Randomization		X[a]
Physical examination		X[a]
Weight		X
Assessment of AEs/SAEs	X	X
Concomitant medications	X	X
Vital signs	X	X[b]
Blood collection for:		
Serum chemistry and hematology	X	
PK blood sample		X[c]
IM blood sample		X[c]
Serum biomarkers		X[c]
Pregnancy test (serum βHCG)	X	
Urine collection for:		
Urinalysis	X	
Urine drug screen	X	
Investigational product administration (300 mg tralokinumab)		**X**
Assessment of injection site for:		
Fluid leakage and gravimetric analysis		X[d]
Pain intensity via VAS		X[e]
Pruritus via VAS		X[e]

Table 4.2.2-1 Schedule of Treatment Procedures

Study Period	Admission to Study Unit	Treatment
Visit Number	**V2**	**V2**
Procedure / Study Day or Week	**Day -1**	**Day 1**
Local injection-site reactions [f]		X [g]

AE = adverse event; βHCG = beta-human chorionic gonadotrophin; eCRF = electronic case report form; IM = immunogenicity; PK = pharmacokinetic; SAE = serious adverse event; V = visit; VAS = visual analogue scale.

[a] Prior to investigational product administration

[b] Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed prior to, immediately post-injection, and at 10, 30, 60 minutes, and 4 and 8 hours after administration

[c] Serum samples for PK, immunogenicity, and biomarkers will be collected immediately (within 30 minutes) prior to administration of investigational product

[d] Assess for fluid leakage immediately post-injection

[e] Both pain intensity and pruritus at injection site will be assessed by the subject immediately post-injection, once the needle insertion set has been withdrawn (after the second injection in Cohort 1), and at 10, 20, 30, and 60 minutes and then at 2, 4, and 8 hours post-injection for all 4 cohorts. Assessments for pain intensity only at the injection site will be conducted at 1 and 6 minutes during the injection for Cohort 4 only.

[f] Local injection-site reactions are of specific interest and will be recorded in detail on dedicated and standardized injection site assessment questionnaire (see Appendix 2) at each time point post-injection. These targeted assessment events will not require reporting as AEs on the AE eCRF, unless they meet 1 or more of the following criteria:

- Fulfils the criteria for an SAE
- Leads to premature termination of the injection during investigational product administration
- Requires concomitant medication or other medically important intervention
- Has an impact on the general condition of the subject as judged by the investigator

[g] Local injection site reactions (eg, erythema, bleeding, rash, etc) will be assessed by a blinded assessor immediately post-injection (after the second injection in Cohort 1) and at 10, 20, 30, and 60 minutes and then at 2, 4, and 8 hours post-injection for all 4 cohorts

Table 4.2.2-2 Timing of Day 1 Assessments

Assessment	Prior to IP Admin	During IP Administration		Post IP Administration							
		1 Min (Cohort 4 only)	6 Min (Cohort 4 only)	Immediately	10 Min (~ 3 min)	20 Min (~ 3 min)	30 Min (~ 3 min)	60 Min (~ 3 min)	2 Hours (~ 10 min)	4 Hours (~ 10 min)	8 Hours (~ 10 min)
Randomization	X										
Physical examination	X										
Weight	X										
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X			X	X		X	X		X	X
Collect blood for:											
PK	X										
IM	X										
Biomarkers	X										
Assess injection site[a] for:											
Fluid leakage/ gravimetric analysis				X							
Pain intensity via VAS		X	X	X	X	X	X	X	X	X	X
Pruritus via VAS				X	X	X	X	X	X	X	X
Local injection-site reactions[b]				X	X	X	X	X	X	X	X

Admin = administration; AE = adverse event; IM = immunogenicity; IP = investigational product; Min/min = minute(s); PK = pharmacokinetic; SAE = serious adverse event; VAS = visual analog scale.

[a] Injection sites must be assessed in the following order at *all time points* post administration of IP: visual inspection for fluid leakage (immediately post-injection only); VAS scale for pain intensity; VAS scale for pruritus; assessment for local injection-site reactions as outlined in Table 4.2.2-2.

[b] Local injection-site reactions to be evaluated by blinded assessor.

4.2.3 Follow-up Period

Table 4.2.3-1 shows all procedures to be conducted during the follow-up period.

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs, then blood draws. For assessment of injection-site reactions, these should be done in the order specified in the table.

Table 4.2.3-1 Schedule of Follow-up Procedures

Study Period	Follow-up								
Visit Number	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**
Procedure / Study Day or Week	**Day 2**	**Day 4**	**Day 6**	**Day 8**	**Day 10 (~ 1 d)**	**Day 15 (~ 1 d)**	**Day 22 (~ 2 d)**	**Day 36 (~ 2 d)**	**Day 57 (~ 2 d)**
Physical examination									X
Weight									X
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Vital signs									X
Blood collection for:									
Serum chemistry and hematology				X		X		X	X
PK blood sample	X [a]	X	X	X	X	X	X	X	X
IM blood sample									X
Serum biomarkers				X				X	X
Urine collection for:									
Urinalysis									X
Assessment of injection site for:									
Pain intensity via VAS	X [b]	X [c, d]							
Pruritus via VAS	X [b]	X [c, d]							
Local injection site reactions	X [b]	X [c, d]							

AE = adverse event; d = day; IM = immunogenicity; PK = pharmacokinetic; SAE = serious adverse event; V = visit; VAS = visual analogue scale.

[a] PK sample to be collected at 24 hours (~ 30 minutes) relative to administration time on Day 1

[b] For each subject, measurements to be taken at 24 hours (Day 2; ~ 1 hour) relative to administration time

[c] For each subject, measurements to be taken at 72 hours (~ 1 hour) relative to administration time

[d] Symptoms and/or signs at the injection site persisting beyond 72 hours will be followed through resolution

4.3 Description of Study Procedures

4.3.1 Efficacy

Efficacy parameters will not be evaluated in this study.

4.3.2 Medical History and Physical Examination, Electrocardiogram, Weight, and Vital Signs

4.3.2.1 Medical 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.

4.3.2.2 Physical Examination, Height, and Weight

Physical examinations, including weight 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. Each clinically significant abnormal finding will be recorded. Physical examinations will be performed at screening and on Days 1 and 57 as outlined in Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1. Weight will be measured at screening and on Days 1 and 57. Height will be measured at screening only.

4.3.2.3 Vital Signs

Vital signs (blood pressure [BP], heart rate, respiratory rate, and body temperature) will be obtained at screening and on Days -1, 1, and 57 as outlined in Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1.

Day 1, vital signs (BP, heart rate, respiratory rate, and body temperature) will be assessed prior to, immediately after, and at 10, 30, and 60 minutes (~ 3 minutes), and 4 and 8 hours (~ 10 minutes) after administration of investigational product within each cohort. Discharge from site will be determined by the investigator.

All vital sign measurements will be made with the subject in a semi-supine position having rested in this position for at least 5 minutes before each reading.

4.3.2.4 Electrocardiogram

A 12-lead ECG will be obtained after 10 minutes supine rest at screening only as outlined in Table 4.2.1-1. Each lead will be recorded for at least 3-5 beats at a speed of 25 mm/second paper speed and 10 mm/mV amplitude. In addition, a 10-second paper ECG print-out from the 12-lead ECGs will be taken at screening and recorded.

Skin preparation should be thorough and electrode positions should be according to standard 12-lead ECG placement.

In this study, lead V2 will be analyzed and reported as primary. Lead V5 will be analyzed, as backup for the individual subject where analysis in lead V2 is not deemed possible.

The following variables will be reported: heart rate, RR, PR, QRS, and QT and QTc intervals from the primary lead of the digital 12-lead ECG. The Principal Investigator or designated sub-investigator will be responsible for the overall interpretation and determination of the clinical significance of any potential ECG findings.

The investigator may add extra 12-lead ECG safety assessments at any time point during the study if there are any abnormal findings, or if the investigator considers it is required for any other safety reason.

4.3.3 Injection Site Assessments

The injection site(s) will be assessed for pain intensity, pruritus, local injection-site reactions, and fluid leakage. For Cohort 1, assessments will begin after the second 1 mL injection has been administered. The subject will assess injection-site pain intensity and pruritus using a VAS as described in Section 4.3.3.2 and Section 4.3.3.3 and a blinded assessor will assess local injection site reactions as described in Section 4.3.3.4. The investigator or qualified designee will assess investigational product leakage as described in Section 4.3.3.1.

4.3.3.1 Investigational Product Leakage

The investigator or qualified designee will visually examine the injection site for investigational product leakage immediately following the injection, once the needle insertion set has been withdrawn, on Day 1 as outlined in Table 4.2.2-1 and Table 4.2.2-2.

If leakage is present, the injection site will be blotted with pre-weighed absorbent material and the amount of leakage will be quantified and recorded. For subjects in Cohort 1 who will receive 2 × 1 mL injections of tralokinumab, the overall assessment of fluid leakage from both injection sites combined should be recorded immediately post-injection.

4.3.3.2 Assessment of Injection-site Pain Intensity

Each subject will assess pain intensity at the injection site using a 100 mm VAS immediately post-injection, once the needle insertion set has been withdrawn (after the second injection in Cohort 1), and at 10, 20, 30, and 60 minutes (~ 3 minutes), and then at 2, 4, and 8 hours (~ 10 minutes), and 24 and 72 hours (± 1 hour) post-injection for all 4 cohorts. For subjects in Cohort 1 who will receive 2 × 1 mL injections of tralokinumab, the overall assessment of pain intensity from both injection sites combined should be recorded at each time point post-injection. Assessments for injection site pain intensity will also be performed at 1 and 6 minutes during the injection in Cohort 4 given the prolonged injection time (12 minutes) as outlined in Table 4.2.2-1 and Table 4.2.2-2.

The 100 mm VAS for assessment of injection site pain intensity is an ungraduated scale where 0 = “no pain” and 100 = “worst imaginable pain” as described in Appendix 4.

4.3.3.3 Assessment of Injection-site Pruritus

Each subject will assess pruritus at the injection site using a 100 mm VAS immediately post-injection, once the needle insertion set has been withdrawn (after the second injection in Cohort 1), and at 10, 20, 30, and 60 minutes (~ 3 minutes), and then at 2, 4, and 8 hours (~ 10 minutes), 24 hours (± 1 hour), and 72 hours (~ 1 hour) post-injection for all 4 cohorts as outlined in Table 4.2.2-1, Table 4.2.2-2, and Table 4.2.3-1. For subjects in Cohort 1 who will receive 2 × 1 mL injections of tralokinumab, the overall assessment of pruritus from both injection sites combined should be recorded at each time point post-injection.

The 100 mm VAS for assessment of injection site pruritus is an ungraduated scale where 0 = “no itch” and 100 = “worst imaginable itch” as described in Appendix 5.

4.3.3.4 Local Injection-site Reactions

Local injection site reactions will be assessed by a blinded assessor (see Section 4.6.2) immediately post-injection, once the needle insertion set has been withdrawn (after the second injection in Cohort 1), and at 10, 20, 30, and 60 minutes (~ 3 minutes), and then at 2, 4, and 8 hours (~ 10 minutes), and 24 and 72 hours (± 1 hour) post-injection for all 4 cohorts as outlined in Table 4.2.2-1, Table 4.2.2-2, and Table 4.2.3-1.

The blinded assessor will assess the injection site at each time point post-injection for the presence or absence of signs and/or symptoms of local injection site reaction, including erythema, hematoma or bleeding, local warmth, swelling, and/or rash. In the case of

injection-site rashes, reference should be made to the definitions of rash morphology descriptors found in Appendix 3.

For subjects in Cohort 1 who will receive 2 × 1 mL injections of tralokinumab, an overall assessment of both injection sites should be recorded at each time point post-injection. Where there are differences in injection site reactions between the two sites for a particular subject, the most severe reaction should always be recorded.

As local injection-site reactions are of specific interest, they will be recorded in detail on a dedicated and standardized injection site assessment questionnaire (Appendix 2) at each time point post-injection. These targeted assessment events will not require reporting as AEs on the AE eCRF, unless they meet 1 or more of the following criteria:

- Fulfils the criteria for an SAE
- Leads to premature termination of the injection during investigational product administration
- Requires concomitant medication or other medically important intervention
- Has an impact on the general condition of the subject as judged by the investigator

Any injection-site reactions that are ongoing beyond 72 hours will be followed up to resolution and the signs/symptoms will be recorded on a local injection-site assessment questionnaire (Appendix 2) at each subsequent visit.

4.3.4 Clinical Laboratory Tests

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.

Clinical laboratory safety tests including serum pregnancy tests will be performed in a licensed central clinical laboratory. Abnormal laboratory results that are considered clinically relevant by the investigator should be repeated as soon as possible (preferably within 24 to 48 hours). Subjects do not need to be fasting prior to collection of blood samples.

The following clinical laboratory tests will be performed (see Table 4.2.1-1, Table 4.2.2-1, and Table 4.2.3-1 for the schedule of tests):

Serum Chemistry

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

Note for serum chemistries: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently.

Hematology

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hematocrit
- Hemoglobin
- Platelet count
- Prothrombin time (PT; screening only)
- Activated partial thromboplastin time (aPTT; screening only)
- Differential blood count
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Blood
- Leucocyte esterase
- Bilirubin
- Urobilinogen
- Nitrite
- Urine microscopy and urine casts (as required)
- Urine culture (as required)
- Urine drug screen (Visits 1 and 2)

Note: Urinalysis for specific gravity, pH, protein, glucose, ketones, blood, and bilirubin may be performed at the site using a licensed test (dipstick).

Pregnancy Test (females of childbearing potential only)

- Serum beta human chorionic gonadotropin (~HCG; at screening and Day -1)

Other Safety Tests

- Hepatitis B surface antigen, hepatitis C antibody (screening only)
- Human immunodeficiency virus-1, -2 (HIV-1,-2) antibody (screening only)

4.3.5 Pharmacokinetic Evaluation and Methods

Blood samples for PK will be taken immediately (within 30 minutes) prior to administration of investigational product on Day 1, at 24 hours (Day 2; ± 30 minutes), and on Days 4, 6, 8, 10, 15, 22, 36, and 57 after dosing to determine the PK profile of tralokinumab (see Table 4.2.2-1 and Table 4.2.3-1). Tralokinumab serum concentrations will be measured by a validated immunoassay method on Gyrolab platform.

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

4.3.6 Immunogenicity Evaluation and Methods

Blood samples will be collected for the assessment of ADA against tralokinumab on Day 1 immediately (within 30 minutes) prior to administration of investigational product and on Day 57 as outlined in Table 4.2.2-1 and Table 4.2.3-1. Samples will be measured for the presence of ADA using a validated method.

4.3.7 Biomarker Evaluation and Methods

4.3.7.1 Serum Biomarkers

Blood samples will be collected for the assessment of serum biomarkers (including periostin and DPP-4) that are relevant to the mechanism of action of tralokinumab immediately (within 30 minutes) prior to administration of investigational product on Day 1, and on Days 8, 36, and 57 as outlined in Table 4.2.2-1 and Table 4.2.3-1.

4.3.8 Estimate of Volume of Blood to Be Collected

The estimated volume of blood to be collected from each subject at each visit (and across all visits) from screening through Day 57 is presented in Table 4.3.8-1. If repeats of any blood tests are required, the volume of blood collection will increase accordingly.

Table 4.3.8-1 Estimate of Blood Volume to be Collected

Visit Day	Estimated Blood Volume (mL)
Day -21 to Day -1 (Visit 1)	17
Day -1 (Visit 2)	12.5
Day 1 (Visit 2)	10
Day 2 (Visit 3)	2
Day 4 (Visit 4)	2
Day 6 (Visit 5)	2
Day 8 (Visit 6)	19.5
Day 10 (Visit 7)	2
Day 15 (Visit 8)	14.5
Day 22 (Visit 9)	2
Day 36 (Visit 10)	19.5
Day 57 (Visit 11)	22.5
Total	**125.5**

4.4 Study Suspension or Termination

The sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
2. Subject enrollment is unsatisfactory
3. Non-compliance that might significantly jeopardize the validity or integrity of the study
4. Sponsor decision to terminate development
5. Sponsor decision to terminate the study based on a planned futility analysis

If MedImmune determines that temporary suspension or termination of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, MedImmune will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must

inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.4.1 Study-stopping Criteria

If the sponsor receives a report of an event that is consistent with any of the following 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. A prompt review of the data will be initiated by the sponsor and the information will be referred to the MedImmune Safety Review Board (MSRB) within 1 business day of the receipt of the initial report by the sponsor. If an event occurs that in the opinion of the MSRB contraindicates further dosing of additional subjects, administration of tralokinumab will be stopped and no additional subjects will be enrolled into the study until further evaluation. The medical monitor will ensure that relevant safety information is distributed to MedImmune Patient Safety as appropriate. The following are criteria for stopping the study:

1. Death in any subject in which the cause of death is assessed as related to tralokinumab
2. Events that in the opinion of the medical monitor and the MSRB contraindicate further dosing of additional subjects, including anaphylaxis (as defined in Appendix 7) requiring treatment with epinephrine and assessed as related to tralokinumab

In addition, any unforeseen events that, in the opinion of the medical monitor contraindicate further dosing of additional subjects may result in interruption of the study and cessation of further dosing of tralokinumab. If the study is interrupted, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted (within 7 working days) to determine if dosing should be resumed, if the study or the protocol should be modified, or if the study will be permanently discontinued. Review and approval by the MSRB will be required before the study may be resumed in the event that the study was interrupted for one of the study-stopping criteria. Where applicable, regulatory authorities and the IRB will be notified of any actions taken. Any subjects who have already received investigational product and are currently enrolled in the study at the time study-stopping criteria are met will continue to be followed by the investigator for safety.

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

MedImmune will provide the investigator(s) with investigational product (Table 4.5-1) using designated distribution centers.

Table 4.5-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Tralokinumab (CAT-354)	MedImmune	

w/v = weight per volume.

Investigational product will be supplied to the site in vials with identical appearances in coded kits. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each vial within the carton).

4.5.1.1 Investigational Product Dose Preparation

Instructions for preparation of the investigational product are provided in Section 4.5.1.4.

4.5.1.2 Dose Calculation

No dose calculation is required for this study.

4.5.1.3 Investigational Product Inspection

Each vial selected for dose preparation should be inspected. Tralokinumab is supplied as a sterile liquid formulation at a concentration of 150 mg tralokinumab per vial (nominal in 1.0 mL) intended for parenteral administration.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section for further instructions.

4.5.1.4 Dose Preparation Steps

No incompatibilities between tralokinumab and dosage administration components (ie, syringe, extension set, and SC insertion set) have been observed.

The unblinded investigational product manager will be responsible for preparing the SC doses using the steps outlined below:

1. All vials of investigational product **must** be equilibrated to room temperature for a minimum of 30 minutes prior to dose preparation
2. The investigational dose volume plus an additional 1.5 mL of dose volume to account for losses in the administration set should be removed from the vials using a 10 mL Becton, Dickinson, and Company (BD) Luer-Lok™ syringe following aseptic technique (see Table 4.5.1.4-1)
3. It is recommended that a 19 gauge (G) × 1 1/2" hypodermic needle be used to withdraw the investigational product dose volume from the vials

Table 4.5.1.4-1 Dose Preparation Summary

Cohort	Total Dose Volume
1	2 × 2.5 mL
2	1 × 3.5 mL
3	1 × 3.5 mL
4	1 × 3.5 mL

Tralokinumab does not contain preservatives and any unused portion must be discarded. Preparation of investigational product syringe is to be performed aseptically. Total in-use storage time from preparation of investigational product/needle puncture of the investigational product vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If storage time exceeds these limits, a new dose must be prepared from new vials.

4.5.1.5 Treatment Administration

The day of dosing is considered Day 1. In each cohort, subjects will receive a single SC dose of 300 mg tralokinumab administered as 2 × 1 mL injections at a flow rate of 6 mL/min (for each injection; Cohort 1), or 1 × 2 mL injection at flow rates of 12, 2, or 0.167 mL/min (Cohorts 2, 3, or 4, respectively).

The investigational product will be administered into the abdomen via the SC route using a syringe pump (Harvard PHD Ultra infuse/withdraw [703006]). For Cohort 1, two separate injection sites will be used for each injection. The injections will be administered concurrently on the same side of the abdomen and spaced at least 3 cm apart. The time of the first SC injection for each subject in Cohort 1 will be recorded.

The fluid path consists of sterile, 510(k)-cleared components attached together via Luer-Lok connections. Specific dosage administration components include the following:

- 10 mL plastic Luer-Lok syringe (BD; 309604)
- Microbore extension set (B Braun; V6203)

- 25 G x $^{1}/_{4}$" Surflo® winged infusion set with 8" tubing (Tenuno; SV*25EL)
- Inset infusion system 6 mm cannula 23" tubing (Unomedical [Animas]; 100-182-00)

The BD 10 mL plastic syringe and B Braun microbore extension set will be used for all cohorts. The following SC insertion sets will be used per cohort:

- Cohorts 1 and 2: Terumo 25 G x Surflo winged infusion set with 8" tubing
- Cohorts 3 and 4: Animas Inset infusion system 6 mm cannula 23" tubing.

The fluid path should be primed using 1 mL dosing volume at an infusion rate of 2 mL/minute before administration for all cohorts.

Preparation and Administration

The following steps are to be followed in preparing the needle insertion site and administering investigational product:

1. The skin surface of the needle insertion site should be wiped with alcohol and allowed to air diy.
2. For Cohorts 1 and 2:
    a. Pinch the skin to isolate the SC tissue from the muscle and insert the needle at a 45-degree angle.
    b. Place a small piece of folded gauze under the winged infusion set to maintain the needle angle.
    c. Tape the winged infusion set in place to minimize needle movement during the course of the injection.
3. For Cohorts 3 and 4: Follow the manufacturer's instructions for applying the Inset infusion system and insert the soft cannula at a 90-degree angle into the SC tissue.
4. Inject the investigational product into the SC tissue using the syringe pump at the flow rates specified for each cohort.
5. Keep the needle in place for **10 seconds** after the syringe pump has stopped delivering investigational product and prior to needle withdrawal.
6. ***Do not*** massage the injection site following the injection.
7. Some investigational product may remain in the syringe, extension set, and infusion set after the infusion is completed.
8. All injection-site assessments are to start after needle has been withdrawn.

If any of the following should occur, the investigator should reschedule the visit and investigational product should not be administered:

- The subject has an intercurrent illness that in the opinion of the investigator and/or medical monitor may compromise the safety of the subject in the study (eg, viral illnesses)
- The subject is febrile (≥ 38°C; ≥ 100.4°F) within 72 hours prior to investigational product administration

Injection site(s) will be assessed immediately post-injection, once the needle insertion set has been withdrawn, and at 10, 20, 30, and 60 minutes and then at 2, 4, 8, 24, and 72 hours post-injection as described in Section 4.3.3. For Cohort 1, assessments will be done after the second injection has been administered. At each time point the blinded assessor will complete the injection site assessment questionnaire; but will not complete an AE eCRF for injection-site reactions, unless the reaction meets one of the following criteria:

- Fulfils the criteria for an SAE
- Leads to premature termination of the injection during investigational product administration
- Requires concomitant medication or other medically important intervention
- Has an impact on the general condition of the subject as judged by the investigator

Injection-site reactions persisting beyond 72 hours will be followed up to resolution.

4.5.1.6 Monitoring of Dose Administration

Vital signs (BP, heart rate, respiratory rate, and body temperature) will be obtained before investigational product administration. After investigational product administration, subjects will be monitored for immediate drug reactions; vital signs will be taken immediately, and at 10, 30, 60 minutes, and 4 and 8 hours after administration of investigational product. Discharge from the site on Day 1 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, immunoglobulin G [IgG] and immune complex mediated]) and nonimmunologic (Johansson et al, 2004). The clinical criteria for defining anaphylaxis for this study are listed in Appendix 7. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Appendix 8. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc, and medical equipment to treat acute anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognize and treat anaphylaxis according to local guidelines.

4.5.1.7 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* **to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.**

MedImmune contact information for reporting product complaints:

[redacted]

4.5.2 Additional Study Medications

No other study medications are specified for use in this clinical protocol.

4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The label will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local languages, as required.

4.5.4 Storage

Store investigational product at 2°C to 8°C.

4.5.5 Treatment Compliance

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

4.5.6 Accountability

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 unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

Subjects will be randomized in a 1:1:1:1 ratio to 1 of 4 cohorts to receive a single SC dose of 300 mg tralokinumab on Day 1 administered as either 2 × 1 mL injections at a flow rate of 6 mL/min for each injection (Cohort 1) or a 1 × 2 mL injection at flow rates of 12, 2, or 0.167 mL/min (Cohorts 2, 3, or 4, respectively). Randomization will be stratified by gender. A minimum of 5 males and 5 females will be randomized to each cohort; the additional subjects may be of either sex. The allocation to each cohort will be open label. Only the injection-site assessor will be blinded to treatment allocation of all subjects (except those randomized to Cohort 1 due to the requirement for 2 separate injections).

The procedure for randomization will be as follows:

1. On Day 1, the investigator or designee will confirm subject eligibility.
2. The SID number and gender will be communicated to the pharmacist/designee.
3. The pharmacist/designee will use a randomization list to assign a randomization number and dispense the investigational product to the subject.
4. The site team will record the appropriate information in the subject's medical records. The pharmacist/designee will maintain a master investigational product accountability log and batch preparation records.

Investigational product (tralokinumab) 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.

4.6.2 Methods for Ensuring Blinding

Both site and sponsor personnel will be unblinded, with the exception of a blinded injection-site assessor who will evaluate local reactions to investigational product administration. The blinded injection-site assessor will be unaware of the treatment allocation

of all subjects where practicably possible (eg, for subjects randomized to Cohort 1, the requirement for 2 separate injections makes blinding to treatment allocation impossible) and will not observe the preparation or administration of investigational product or participate in the conduct of the study outside of the injection-site assessments (see Section 4.3.3.4).

4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including over-the-counter, herbal, and vitamin preparations, taken during the study will be recorded in the eCRF.

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care or to treat AEs as deemed necessary, except for those medications identified as “excluded” as listed in Section 4.7.2. Specifically, subjects should receive full supportive care during the study and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. All concomitant medications used by the subject from screening through Day 57 will be recorded.

4.7.2 Prohibited Concomitant Medications

The use of regular concomitant medications during the study (except those described in Sections 4.5.2), including over-the-counter medications, herbal supplements, and vitamins is discouraged and should be discussed in advance with the sponsor’s medical monitor.

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 medications during the study:

1. Immunosuppressive medication (eg, methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine, oral corticosteroid dose > 10 mg/day prednisone [or equivalent], intramuscular long-acting depot corticosteroid)
2. Oral corticosteroid burst or short-acting systemic corticosteroid; except for the treatment of any allergic reaction, including anaphylaxis
3. Investigational agents
4. Marketed biologics, including omalizumab
5. Immunoglobulin or blood products
6. Use of any oral or ophthalmic ~-adrenergic antagonist (eg, propranolol)

7. Live attenuated vaccines

4.8 Statistical Evaluation

4.8.1 General Considerations

Data will be provided in data listings sorted by SID number. 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. Details of endpoint analyses will be described in the statistical analysis plan (SAP).

Analysis Populations

The PK population is defined as all subjects in the as-treated population with at least one detectable tralokinumab serum concentration and for whom the PK parameters can be adequately estimated.

The as-treated population includes all subjects who receive any amount of investigational product. Subjects will be included in the as-treated population according to the injection flow rate received, even if different from that to which the subject was randomized. Demographics, safety and tolerability endpoints, and biomarkers will be summarized based on the as-treated population.

4.8.2 Sample Size and Power Calculations

The number of subjects planned for this study is based on the number required to obtain adequate PK data while exposing as few healthy volunteer subjects as possible to tralokinumab and procedures. A total of 15 subjects per treatment arm is considered sufficient to detect an approximately 1.5-fold difference in PK parameters between cohorts and will provide exploratory information regarding local tolerability.

A previous single-dose study investigating the PK of tralokinumab (Study CD-RI-CAT-354-1054) showed a coefficient of variation (CV) of 37% for area under the serum concentration-time curve from zero to infinity $(AUC_{0-\infty})$. Assuming the same CV across the cohorts and using a two-sided two-sample t-test at a significance level of 0.05, with 15 subjects per cohort the study will be 84% powered to detect a 1.5-fold difference in $AUC_{0-\infty}$ between Cohort 1 and any of the other treatment cohorts.

4.8.3 Pharmacokinetics

The primary endpoint for this study is PK parameters. Using the serum concentrations of tralokinumab, the PK of tralokinumab will be analyzed using the noncompartmental method as implemented in Phoenix WinNonlin® version 6.3 or higher.

The following PK parameters will be estimated by noncompartmental analysis: $AUC_{(0-\infty)}$; AUC to last observation (AUC_{0-t}); C_{max}; time to C_{max} (T_{max}); terminal-phase half-life ($t_{1/2}$); apparent systemic clearance (CL/F); apparent terminal-phase volume of distribution (Vz/F).

Descriptive statistics for serum tralokinumab concentration data for the PK population will be provided by cohort and will include N, arithmetic mean, standard deviation (SD), percent CV, median, minimum, and maximum.

4.8.4 Safety and Tolerability

4.8.4.1 Analysis of Investigational Product Fluid Leakage

The degree of injection site leakage following injections of 300 mg tralokinumab will be recorded and summarized by cohort; no statistical analysis will be applied.

4.8.4.2 Analysis of Injection-site Pain Intensity

Visual analogue scale values for injection site pain intensity will be summarized for each cohort at each time point using descriptive statistics. The distribution of the pain intensity scores will be examined and the between-cohort difference will be explored.

4.8.4.3 Analysis of Injection-site Pruritus

Visual analogue scale values for injection site pruritus will be summarized for each cohort at each time point using descriptive statistics. The distribution of the pruritus scores will be examined and the between-cohort difference will be explored.

4.8.4.4 Analysis of Local Injection-site Reactions

Local injection site reactions will be recorded on a specific questionnaire (Appendix 2) by the blinded assessor and will be summarized by descriptive statistics by cohort over time.

4.8.4.5 Analysis of Overall Safety Profile

The safety profile of tralokinumab will be assessed at completion of the study primarily by summarizing TEAEs including treatment-emergent serious adverse events (TESAEs). All TEAEs, including TESAEs, will be summarized by system organ class and preferred term,

by severity, and by relationship to the investigational product. The occurrence of TEAEs to tralokinumab will be collected and summarized from the start of the tralokinumab injection on Day 1 through the end of study (Day 57). No formal statistical analysis will be applied.

Laboratory measurements as well as their changes from baseline at each collection time point and shift from baseline, if applicable, will be summarized descriptively. Significant vital sign measurements and physical examination findings will also be summarized using descriptive analyses. No formal statistical analysis will be applied.

4.8.5 Analysis of Immunogenicity

The immunogenicity of tralokinumab will be evaluated. The number and percentage of subjects with confirmed positive serum antibodies to tralokinumab will be reported by cohort. If possible, the incidence of ADA positivity will be correlated with the observed PK.

4.8.6 Analysis of Serum Biomarkers

Serum biomarkers (including periostin and DPP-4) will be summarized by descriptive statistics by cohort. This analysis will be presented separately by the sponsor.

4.8.7 Interim Analysis

No interim analyses are planned.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

The International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) 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 ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure,

hematuria), not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

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.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- 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.

5.3 Definition of Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

Hepatic function abnormality meeting the definition of Hy's law is considered an AESI. See Section 5.6.2 for the definition and reporting of AESIs of hepatic function abnormality.

5.4 Recording of Adverse Events

Adverse events will be recorded on the eCRF 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 5.2 for the definition of SAEs and Appendix 6 for guidelines for assessment of severity and relationship. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

5.4.1 Local Injection-site Reactions

Local injection site reactions are of specific interest and will be recorded in detail on dedicated and standardized injection site assessment questionnaire (Appendix 2) at each time point post investigational product administration. In the case of injection-site rashes, reference should be made to the definitions of rash morphology descriptors found in Appendix 3. As a result of this targeted assessment, local injection-site reactions will not require reporting as AEs on the AE eCRF unless they meet one or more of the following criteria:

- Fulfils the criteria for an SAE
- Leads to premature termination of the injection during investigational product administration
- Requires concomitant medication or other medically important intervention
- Has an impact on the general condition of the subject as judged by the investigator

Where it may help with assessment and interpretation of individual injection-site reactions, anonymized photographs of such reactions may be taken and stored with the source documents. Subjects will be asked to provide specific consent to allow photographs to be taken for this purpose as part of the main consent form.

5.4.2 Time Period for Collection of Adverse Events

Adverse events will be collected from the time signature of informed consent is obtained throughout the treatment period and including the follow-up period at Day 57 (Visit 11).

New non-serious AEs that start after Day 57 (Visit 11) will not be collected. All AEs that start from the time informed consent is signed through the treatment period, including the

follow-up period (Day 57; Visit 11), will be followed to resolution through the end of subject participation in the study.

All SAEs will be recorded from the time informed consent is signed through the end of subject participation in the study (Day 57; Visit 11). After submitting the initial SAE report to MedImmune Patient Safety, the investigator will be required to follow the subject proactively and provide MedImmune Patient Safety with further information regarding the subject's condition.

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

5.4.3 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF.

The investigator is responsible for following all SAEs to resolution, until the subject returns to baseline status, or until the condition has stabilized, with the exception if a condition remains chronic, even if this extends beyond study participation.

MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.5 Reporting 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:

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. 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.

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the IB, 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 5.5 for contact information). If the overdose results in an AE, the AE must also be recorded on the AE eCRF (see Section 5.4). 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 recorded and reported as an SAE (see Section 5.4 and Section 5.5, respectively). MedImmune does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

5.6.2 Hepatic Function Abnormality

Adverse events of hepatic function abnormality of special interest to the sponsor are defined as any increase in ALT or AST to greater than 3 × ULN **and concurrent** increase in bilirubin to greater than 2 × ULN (ie, Hy's law cases). Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event.

If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease), the diagnosis should be recorded as an AE/SAE.

If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE.

Hepatic function abnormality of unknown etiology, or which is considered attributable to investigational product, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the SAE Report Form, even if the event is considered to be non-serious (see Section 5.5 for contact information). The investigator will review the data with the medical monitor. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

- If, after appropriate workup, in the opinion of the investigator, the underlying diagnosis for the abnormality remains unexplained, or is considered attributable to investigational product, dosing of the study subject should be permanently discontinued.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor.

5.6.3 Pregnancy

Pregnancy in a female 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 5.5 for contact information).

Subjects who become pregnant during the study will be withdrawn from the study. 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.

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product this should be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 5.5 for contact information). The sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

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

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

6.2 Monitoring of the Study

During the study, a MedImmune representative will have regular contact with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the laboratory manual and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject

The MedImmune representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

6.2.2 Study Agreements

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

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

6.2.3 Archiving of Study Documents

The investigator follows the principles outlined in the Clinical Study Agreement.

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through the last protocol-specified visit/assessment, 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 4.1.5 and Section 4.1.6).

The end of the study (“study completion”) is defined as the date of the last protocol-specified visit/assessment for the last subject in the study.

6.4 Data Management

Data management will be performed by MedImmune Data Management staff or other party according to the Data Management Plan.

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

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

6.5 Medical Monitor Coverage

Each subject will be provided with contact information for the Principal Investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergency situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the principal investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third party vendor.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, and applicable regulatory requirements.

7.2 Subject Data Protection

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

7.3 Ethics and Regulatory Review

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

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to MedImmune before enrollment of any subject into the study.

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

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

If required by local regulations, the protocol should be re-approved by the IRB/IEC annually.

Before enrollment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

MedImmune will handle the distribution of any of these documents to the national regulatory authorities.

MedImmune will provide regulatory authorities, IRB/IEC and Principal Investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant.

Each Principal Investigator is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. MedImmune will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

7.4 Informed Consent

The Principal Investigator will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the Informed Consent Form that is approved by an IRB/IEC

7.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and MedImmune.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

The amendment is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

MedImmune will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IRB/IEC see Section 7.3.

If a protocol amendment requires a change to a site's Informed Consent Form, MedImmune and the site's IRB/IEC are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB/IEC.

7.6 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

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Appendix 1 Signatures

Signature of Principal Investigator

A Phase 1 Study to Evaluate the Pharmacokinetics and Tolerability of a Single Subcutaneous Dose of Tralokinumab When Delivered as a 2 mL Injection at Different Flow Rates to Healthy Volunteers

I, the undersigned, have reviewed this protocol, 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.

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Appendix 3 Definitions of Injection-site Rash Morphology

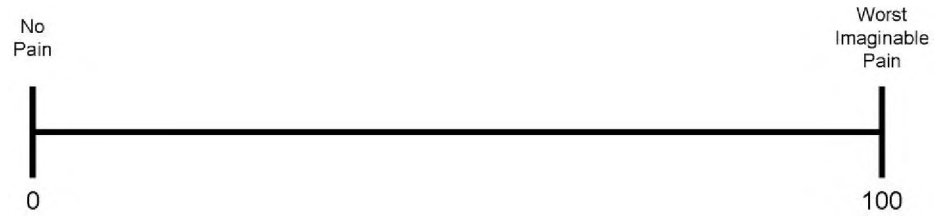
The following table of definitions to be used in conjunction with the injection-site assessment questionnaire (Appendix 2):

Table 8-1 Definitions of Injection-site Rash Morphology

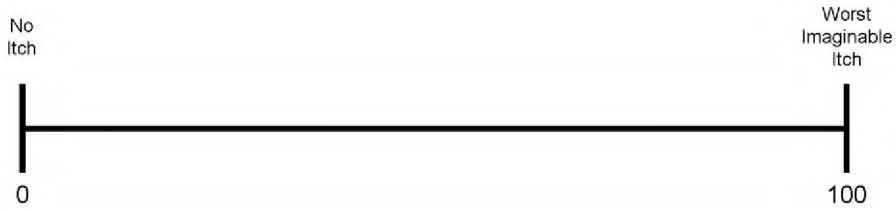
Rash Type	Description
Macule	A flat area of skin or mucous membranes with different color or texture from surrounding tissue, < 0.5 cm diameter
Papule	A discrete, solid, elevated lesion, < 0.5 cm in diameter
Morbilliform	A lesion that has both macular and papular features
Plaque	A discrete, solid, elevated lesion usually broader than it is thick, measuring > 0.5 cm in diameter
Pustule	A superficial vesicle containing a cloudy or purulent fluid
Vesicle	A fluid-filled cavity or elevation < 1 cm in diameter. Fluid can be clear, serous, hemorrhagic, or pus-filled
Bulla	A fluid-filled cavity or elevation ≥ 1 cm in diameter. Fluid can be clear, serous, hemorrhagic, or pus-filled
Wheal (hive)	An edematous, transitory papule or plaque

Source: Adapted from Beigel et al, 2007 (http://www.brightoncollaboration.org).

Appendix 4 100 mm VAS for Assessment of Injection-site Pain Intensity (Sample)


No
Pain
Worst
Imaginable
Pain
0
100

Appendix 5 100 mm VAS for Assessment of Injection-site Pruritus (Sample)


No
Itch
Worst
Imaginable
Itch
0
100

Appendix 6 Additional Safety Guidance

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 Grades 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 5.2. 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.

Assessment of Relationship

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).

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 TEASEs. 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).

Appendix 7 National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;Feb;117(2):391-7.

The National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

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 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 likely allergen for that patient (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 known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

Appendix 8 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 (eg, 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 Aug;63(8):1061-70.