A Phase 1, Open-label Study to Evaluate the Pharmacokinetics of Tralokinumab in Adolescents with Asthma

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Table of Contents

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List of In-text Tables

List of In-text Figures

List of Appendices

List of Abbreviations

Abbreviation or Specialised Term	Definition
ADA	anti-drug antibodies
AE	adverse event
AHR	airway hyperresponsiveness
ALT	alanine transaminase
ATS	American Thoracic Society
AST	aspartate transaminase
AUC	area under the concentration-time curve
βHCG	beta-human chorionic gonadotrophin
BMI	body mass index
CI	confidence interval
CL	systemic clearance
C_{max}	maximum concentration
CRF	case report form
ECG	electrocardiogram
ERS	European Respiratory Society
EU	European Union
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GINA	Global Initiative for Asthma
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IgG4	immunoglobulin G4
IL-13	interleukin-13
IM	immunogenicity
IV	intravenous

Abbreviation or Specialised Term	Definition
IXRS	interactive voice/web response system
LABA	long-acting beta agonist
MAb	monoclonal antibody
OCS	oral corticosteroids
PEF	peak expiratory flow
PK	pharmacokinetic
SABA	short-acting beta agonist
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SID	subject identification number
SMC	Safety Monitoring Committee
SUSAR	suspected unexpected serious adverse reactions
Th2	T-helper type 2
$t_{1/2}$	half-life
t_{max}	time of occurrence for maximum drug concentration
ULN	upper limit of normal
V_{ss}	volume of distribution

Study Abstract

TITLE

A Phase 1, open-label study to evaluate the pharmacokinetics (PK) of tralokinumab in adolescents with asthma

OBJECTIVES

Primary Objective

To evaluate the PK profile of a single-dose 300 mg subcutaneous (SC) administration of tralokinumab in adolescent subjects with asthma.

Secondary Objectives

1) To evaluate the safety and tolerability of tralokinumab

2) To evaluate the immunogenicity (IM) of tralokinumab

Exploratory Objectives

1) To evaluate the effect of tralokinumab on pulmonary function

STUDY DESIGN

This is a Phase 1, open-label, single-dose study to evaluate the PK profile of tralokinumab in adolescent subjects (12-17 years) with asthma requiring the daily use of controller medications described at Step 2-5 of the Global Initiative for Asthma (GINA) guidelines. A total of 20 subjects will be entered into the study at approximately 4 sites in Europe. Ten subjects will be aged between 12-14 years and 10 subjects will be aged between 15-17 years. All subjects entered into the study will receive a single SC 300 mg dose of tralokinumab.

Subjects will attend the clinic and informed consent will be obtained from the legal representative and informed assent will be obtained from the subject. If the screening assessments are initiated at this consent visit, they must be completed within 14 days. If the screening assessments are not initiated at the consent visit, the subject will return to the clinic within 30 days of this consent visit and will complete their screening assessments within 14 days (Days -14 to -1) before investigational product administration. Subjects will receive a single 300 mg SC dose of tralokinumab on Day 1 and will then return to the clinic up to Day 57 for safety follow-up.

Subjects will be in the study for up to 101 days; including up to 30 days for consent, 14 days for screening and 57 days for safety follow-up.

SUBJECT POPULATION

The subjects in this study will be adolescent subjects (12-17 years) with a diagnosis of asthma for a minimum of 6 months and requiring treatment with the daily use of asthma controller medications described at Steps 2-5 of GINA guidelines (GINA, 2010).

TREATMENT REGIMEN

All 20 subjects will receive a single SC 300 mg dose of tralokinumab on Day 1. Investigational product (tralokinumab) will be administered as 2 SC injections of 1 mL.

ASSESSMENT OF ENDPOINTS The following PK parameters will be estimated by noncompartmental analysis: areas under the time-concentration curves from zero to infinity and to last observation ($AUC_{(0\text{-infinity})}$; $AUC_{(0\text{-t})}$); dose-normalized $AUC_{(0\text{-infinity})}$ ($AUC_{(0\text{-infinity})}/D$); C_{max}; dose-normalized C_{max} (C_{max}/D); time to C_{max} (T_{max}); terminal-phase elimination half-life ($t_{1/2}$); apparent clearance (CL/F); steady-state volume of distribution (Vss/F).

The safety and tolerability of a single-dose SC injection of tralokinumab will be assessed through the incidence of treatment-emergent adverse events, and the assessment of vital signs, physical examinations, laboratory

parameters, and electrocardiogram.

Immunogenicity of tralokinumab will be evaluated. The incidence rate of positive serum antibodies to tralokinumab will be reported.

The effect of tralokinumab on pulmonary function as measured by prebronchodilator forced expiratory volume in 1 second will be assessed. Change from baseline in the mean values and percent change from baseline at various time points will be summarized using descriptive statistics.

INTERIM ANALYSIS

No interim analyses are planned.

SAMPLE SIZE

The number of subjects has been based on the desire to obtain adequate PK and safety data while exposing as few subjects as possible to tralokinumab and procedures. A total of 20 subjects are considered sufficient to provide adequate information and to ensure that the study includes subjects across the adolescent age range, 10 subjects will be 12-14 years old and 10 subjects will be 15-17 years old.

1 Introduction

1.1 Disease Background

1.1.1 Asthma

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, 2010) recommend inhaled corticosteroids (ICS) as first-line therapy for persistent asthma. For those patients that are symptomatic and on ICS alone, the addition of a long-acting β2-agonist (LABA) is the current treatment of choice. However, there are a number of asthmatic patients who are still symptomatic despite treatment with ICS and LABA combinations (Rabe et al, 2004). Treatment options then include the addition of other controller therapies including leukotriene antagonists, theophylline, and oral glucocorticosteroids. Xolair® (omalizumab) may be suitable for a subgroup of patients with elevated serum immunoglobulin (IgE) levels. The principles of asthma management for adolescents are the same as for adults, namely to maintain asthma control by reducing impairment and risk with the lowest possible doses of medications, employing a stepwise approach to therapy.

Uncontrolled asthma in childhood is associated with increased healthcare utilization and adverse impact on quality of life, and can have long-term effects on lung function, with impairment frequently persisting into adulthood (National Heart, Lung, and Blood Institute, 2007). In the Children and Asthma in America survey of children and adolescents aged 4-18 years with asthma, more than half of the subjects (54%) had at least one sudden, severe asthma attack within the previous 12 months and 19% had a severe attack at least twice within the past year. A total of 42% of children had some form of urgent or emergency care visit for their asthma in the past year. In addition limitations on daily activities were reported in 62% and children in the survey missed an average of 3.7 days of school in the past year with 9% missing more than 2 weeks (Massanari et al, 2009).

There is therefore a clear medical need for therapies to treat childhood asthma, particularly those with severe asthma unable to gain complete asthma control using currently available therapies.

Tralokinumab is an investigational product currently in clinical development for the management of asthma in adults and adolescents. The objectives and the design of this study have been approved by the Paediatric Committee of the European Medicines Agency as part of the tralokinumab Paediatric Investigation Plan.

1.1.2 Role of Interleukin-13 in the Pathogenesis of Asthma

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

- The development of airway hyperresponsiveness (AHR) through the recruitment and activation of inflammatory cells (Wardlaw et al, 1988)
- Increased IgE synthesis and consequent mast cell activation (Kaur et al, 2006)
- Direct effects on airway smooth muscle cells enhancing cell proliferation, and potentiated bronchoconstriction induced by acetylcholine or histamine (Grunstein et al, 2002; Laporte et al, 2001; Lee et al, 2001)
- Regulation of airway inflammation by stimulating the production of the eosinophil chemoattractant C-C motif chemokine ligand-11 (eotaxin-1) and upregulating vascular cell adhesion molecule-1 expression.
- Increasing the numbers of mucus-secreting cells.
- Promoting airway fibrosis in asthma (Wills-Karp et al, 1998).

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

Clinical data have been reported that show an improvement in lung function in adult subjects with moderate to severe asthma following blockade of IL-13 with both tralokinumab and lebrikizumab (Corren et al, 2011), both monoclonal antibodies (MAb) to IL-13, supporting the hypothesis that IL-13 is an important mediator in 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 for tralokinumab.

1.2 Description of Tralokinumab

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

1.2.1 Product Derivation

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

1.2.2 Summary of Nonclinical Experience

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

Toxicology studies were conducted in cynomolgus monkeys following single and repeated intravenous (IV) and subcutaneous (SC) doses of tralokinumab. Following multiple IV doses of up to 100 mg/kg/week tralokinumab (longest administration schedule was weekly for 26 weeks), there were no local or systemic dose-limiting toxicities and a no-observable-adverse-effect-level of 100 mg/kg/week was identified. Repeated SC dose studies in

cynomolgus monkeys showed no local or systemic effects when administered as 4-weekly SC doses up to 225 mg/injection or as 13-weekly doses up to 300 mg/injection.

When reviewing the potential need for juvenile nonclinical safety studies to support clinical development in adolescents, consideration was given to the potential for target organ or systemic toxicity in developing systems, effects on growth and/or development in the intended age group, and pharmacological effects that would affect developing organs. The lack of adverse effects noted in the available tralokinumab nonclinical data, including results from a pilot embryo-foetal study and a pre- and post-natal development study in cynomolgus monkeys in which neonates were monitored for growth and development to approximately 28 days after delivery (100 mg/kg IV), demonstrates that the current tralokinumab nonclinical safety data are supportive of the proposed adolescent study.

1.2.3 Summary of Clinical Experience

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

Study MI-CP199 was a Phase 2a proof of concept study in which tralokinumab (150, 300, or 600 mg) or placebo was administered as a SC injection at 14-day intervals for a total of 7 doses to adult subjects with uncontrolled, moderate-to-severe, persistent asthma. A clinical effect was observed with the addition of SC tralokinumab to standard asthma controller medications in the study. Although the primary endpoint of the study (mean change from baseline in the Asthma Control Questionnaire-6 score comparing the combined tralokinumab groups to placebo) was not met, an increase in prebronchodilator forced expiratory volume in 1 second (FEV_1) was observed at the first scheduled visit (2 weeks) after first dose of tralokinumab. At the primary endpoint, Day 92, the mean increase from baseline FEV_1 was 0.063 L (4.3%) in the placebo group versus 0.210 L (12.5%) in the combined tralokinumab treatment group $p = 0.072$; the increases in FEV_1 from baseline observed for each tralokinumab treatment group were 8.1% (150 mg), 13.3% (300 mg) and 16.1% (600 mg) ($p = 0.299, 0.102, 0.041$ respectively). Across the majority of study timepoints, the magnitude of the increase in FEV_1 was similar in the 300 and 600 mg tralokinumab treatment groups, while smaller improvements were observed in the 150 mg tralokinumab treatment group. Of note, the improvement in airflow obstruction in subjects that received tralokinumab was also

apparent at Day 169 (12 weeks after the final dose of tralokinumab), suggesting a persistence of the treatment effect on this endpoint. Treatment with tralokinumab also showed a trend towards greater increase in change from baseline of forced vital capacity (FVC) and clinic measured peak expiratory flow (PEF) in the combined tralokinumab treatment group compared to the changes in the placebo group, although these differences were not statistically significant. A reduction in the requirement for the use of additional short-acting β2 agonist (SABA) was observed in those subjects that received tralokinumab that was consistent with the observed increase in FEV_1.

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

Two treatment-emergent SAEs have been reported in other clinical studies with tralokinumab; one subject who had received one IV dose of tralokinumab at 5 mg/kg experienced a lower respiratory tract infection, precipitating an exacerbation of asthma (Study CAT-354-0602) that was considered unlikely to be related to investigational product; and one event of acute hypersensitivity reaction was reported in a 30-year-old female subject with a history of asthma and multiple allergies who received a single IV infusion of 10 mg/kg tralokinumab (Study CAT-354-0603) that was considered as related to investigational product.

Population pharmacokinetic (PK) modeling has been conducted using tralokinumab PK data taken from 219 adults from 4 completed studies; the study populations included healthy subjects and subjects with asthma of varying severity. This analysis indicates that baseline body weight is a determinant of tralokinumab PK, not gender, disease status, or race.

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

A Phase 2b study (CD-RI-CAT-354-1049) is ongoing to evaluate 2 SC treatment regimens of 300 mg tralokinumab compared with placebo by assessing the effect on asthma exacerbation rate over 52 weeks in adults with uncontrolled, severe asthma requiring high dose ICS and LABA with or without additional asthma controller medications.

1.3 Research Hypothesis

The hypothesis of this study is that the PK of tralokinumab in an adolescent population (12-17 years) is similar to that in adults. The PK data gathered in this study will be added to a population PK model to assess any PK differences between adolescents and adults and guide dosing for future studies that include adolescents.

1.4 Rationale for Study Conduct

Tralokinumab is an investigational product currently in clinical development for the management of asthma. Studies to date have exclusively enrolled adult subjects; however, future efficacy and safety studies are expected to enroll both adults and adolescents since IL-13 is expected to be an important mediator in both age groups. This study will explore the PK profile of 300 mg SC tralokinumab in adolescent subjects and the resulting data will be compared with PK data from completed studies in adults. It is expected that drug exposure will be comparable between adults and adolescent thereby justifying use of the same fixed SC dose of tralokinumab in future studies of subjects 12 years and above. To ensure that the study includes subjects across the adolescent age range, 10 subjects will be aged 12-14 years and 10 subjects will be aged 15-17 years.

1.5 Benefit-Risk and Ethical Assessment

There is an unmet medical need for new therapies for use in adolescent subjects unable to gain asthma control using standard asthma controller medications. In Study MI-CP199, treatment with tralokinumab in adult subjects showed evidence of an increase in FEV_1 compared with placebo (see Section 1.2.3). It is anticipated that these effects will also be observed in an adolescent population; therefore, further study of tralokinumab as a potential therapeutic asthma controller therapy for adolescent subjects with asthma is warranted. This study will enable future chronic dosing studies that will determine the safety and efficacy profile of tralokinumab in adolescents with asthma.

In the context of this study, the probability of therapeutic benefit following a single dose of tralokinumab cannot be predicted; however, it may be anticipated that subjects will derive benefit from the regular review by healthcare professionals during their participation.

In clinical studies completed to date, tralokinumab was generally well tolerated. A number of possible risks have been identified that are described in the current Investigator Brochure and

appropriate measures are in place in this study to protect participating subjects both through the application of inclusion, exclusion (subjects with uncontrolled asthma are excluded), and study stopping criteria. Subjects will be monitored closely during the study; in the postdosing period, subjects will be monitored for immediate drug reactions with vital signs taken at 15, 30, 45 minutes, and 1, 4, and 8 hours after dosing and subjects will remain at site for a minimum of 8 hours. Thereafter there will be 7 visits in the following 21 day period and a further 2 visits through to Day 57. The study has been designed to minimize intervention while ensuring that the study objectives are met and subjects are adequately protected.

In conclusion, previous clinical experience with tralokinumab has provided both evidence of its potential as a therapeutic asthma controller and an absence of major safety or tolerability concerns. Hence, the current risk/benefit ratio is favorable and justifies the administration of tralokinumab in this study.

2 Study Objectives

2.1 Primary Objective

To evaluate the PK profile of a single-dose 300 mg SC administration of tralokinumab in adolescent subjects with asthma.

2.2 Secondary Objectives

1) To evaluate the safety and tolerability of tralokinumab
2) To evaluate the immunogenicity (IM) of tralokinumab

2.3 Exploratory Objectives

1) To evaluate the effect of tralokinumab on pulmonary function

These data will be reported in the Clinical Study Report.

3 Study Design

3.1 Overview of Study Design

This is a Phase 1, open-label, single-dose study to evaluate the PK profile of tralokinumab in adolescent subjects (12-17 years) with asthma requiring the daily use of controller medications described at Step 2-5 of the GINA guidelines. A total of 20 subjects will be entered into the study at approximately 4 sites in Europe. Ten subjects will be aged between 12-14 years and 10 subjects will be aged between 15-17 years. All subjects entered into the study will receive a single SC 300 mg dose of tralokinumab.

Subjects will attend the clinic and informed consent will be obtained from the legal representative and informed assent will be obtained from the subject. If the screening assessments are initiated at this consent visit, they must be completed within 14 days. If the screening assessments are not initiated at the consent visit, the subject will return to the clinic within 30 days of this consent visit and will complete their screening assessments within 14 days (Days -14 to -1) before investigational product administration. Subjects will receive a single 300 mg SC dose of tralokinumab on Day 1 and will then return to the clinic up to Day 57 for safety follow-up (Figure 3.1-1).

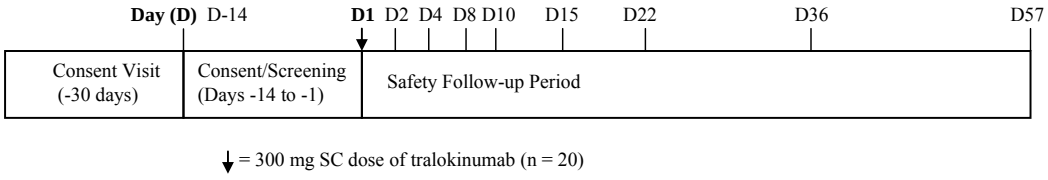

Figure 3.1-1 Study Flow Diagram

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

3.2 Estimated Duration of Subject Participation

Subjects will be in the study for up to 101 days; including up to 30 days for consent, 14 days for screening and 57 days for safety follow-up.

3.3 Study-Stopping Criteria

If the sponsor receives a report of an event 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. If the assessment confirms the event as a study-stopping criterion, further dosing of tralokinumab will be stopped and no additional subjects will be entered into the study. Notification of the event, its assessment, and whether or not the study has been interrupted must be made to the MedImmune Safety Monitoring Committee (SMC) by the medical monitor within 1 business day of the receipt of the initial report by the sponsor.

1) Death in any subject in which the cause of death is assessed as related to tralokinumab.
2) Anaphylactic reaction (immediate life-threatening allergic reaction with bronchoconstriction, angioedema, and/or hypotension) requiring epinephrine in any subject that is assessed as related to tralokinumab.
3) Immune complex disease; a definition of immune complex disease is provided in Appendix 3.

In addition, unforeseen events that in the opinion of the medical monitor and the SMC 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 to determine whether dosing should be resumed, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the MedImmune SMC is required for resumption of the study in the event that the study is interrupted following one of the above-listed events. Where applicable, regulatory authorities and Independent Ethics Committees (IECs) will be notified of any actions taken with the study.

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

Withdrawal criteria for individual subjects are provided in Section 4.2.3.

3.4 Rationale for Study Design, Doses, and Control Groups

This study will evaluate the PK, safety, tolerability, and IM of a single SC injection of 300 mg tralokinumab in adolescent subjects with a diagnosis of asthma for a minimum of 6 months and requiring treatment with the daily use of asthma controller medications described at Steps 2-5 of GINA guidelines (GINA, 2010). It is an open label study with no subjects receiving placebo.

3.4.1 Study Rationale and Choice of Study Population

The principal purpose of this study is to assess the PK of tralokinumab in adolescent subjects and to compare with the PK from studies conducted in adults. It is expected that the PK of tralokinumab in adolescent subjects is similar to that in adults.

Adolescent subjects with a diagnosis of asthma for a minimum of 6 months and requiring treatment with the daily use of asthma controller medications described at Steps 2-5 of GINA guidelines (GINA, 2010) have been chosen as the study population since the PK derived from these subjects will be directly relevant for subsequent safety and efficacy studies in adolescents with asthma.

3.4.2 Justification of Study Design

This study design has been reviewed and approved by the Paediatric Committee of the European Medicines Agency as part of the tralokinumab Paediatric Investigation Plan.

This is an open label study. A placebo group is not considered required for this study since the primary objective is to determine the PK of 300 mg SC tralokinumab and no formal assessment of efficacy will be made. The assessment of the safety and tolerability of tralokinumab can be made without a placebo group.

Each subject will receive a single SC dose of tralokinumab and will be followed for 57 days after investigational product administration. Based on prior data, the maximum concentration (C_{max}) of tralokinumab usually occurs between 2-9 days with a half-life of approximately 21 days after SC administration. The present sampling scheme has 7 PK samples taken within 10 days postdosing and further follow-up samples up to approximately 3 half-lives; thus providing adequate samples for the characterization of C_{max} and area under the serum concentration-time curve (AUC) parameters through a noncompartmental analysis. The

single dose and the subsequent sampling scheme will allow the estimation of PK parameters with adequate precision to achieve the objectives of the study and facilitate the future development of tralokinumab in the adolescent population.

3.4.3 Justification for Primary and Secondary Endpoints

All endpoints are standard for a study of this design. The study assessments and schedule are shown in Table 5.1-1 and are described in Section 5.

3.4.4 Dose Justification and Duration of Treatment

A 300 mg SC tralokinumab dose has been selected as the target dose in the ongoing safety and efficacy study in adults (CD-RI-CAT-354-1049); this choice of dose is supported by observations from Study MI-CP199 in which an increase in FEV_1 and an acceptable safety profile was observed in subjects receiving 300 mg SC tralokinumab, in addition to prestudy asthma controller medications. Population PK modeling has been conducted using tralokinumab PK data taken from 219 adults in 4 completed studies and the resulting simulations support the selection of the 300 mg SC dose in this study. The model predicts that the exposure to tralokinumab after a single SC administration of 300 mg will be similar for adults and adolescents, while increases in C_{max} will be modest (< 1% per kg across the range of adolescent body weight). In addition taking into account that adult subjects with asthma have previously received repeat doses of up to 600 mg SC tralokinumab with an acceptable safety profile, the model predicts that the tralokinumab exposure following administration of 300 mg SC tralokinumab in an adolescent with a minimum body weight at baseline of 30 kg will be approximately 50% less than an adult receiving 600 mg SC tralokinumab, and the C_{max} will be approximately 40% less. The simulations therefore support both the expectation that the PK of tralokinumab in adolescent subjects will be similar to that in adults and also that the 300 mg dose will result in exposures less than those previously well tolerated by adults.

In summary, a SC dose of 300 mg SC is predicted to be well tolerated, while providing valuable information on the PK and safety of tralokinumab in adolescents in the expectation that this dose will be used in future studies that include adolescent subjects.

4 Study Procedures

4.1 Subject Participation and Identification

Study participation begins once written informed consent and written informed assent is obtained (see Section 10.3 for details). Once informed consent/assent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice/web response system, IXRS), and the screening evaluations 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, including the reason(s) for screening failure.

4.2 Subject Selection and Withdrawal

The subjects in this study will be adolescent subjects (12-17 years) with a diagnosis of asthma for a minimum of 6 months and requiring treatment with the daily use of asthma controller medications described at Steps 2-5 of GINA guidelines (GINA, 2010).

The investigator (physician) or qualified designee will discuss the study with a subject considered to be a potential candidate for the study together with his or her legal representative and provide the subject/legal representative with the study-specific informed consent and assent forms approved by the IEC. The investigator or designee will address any questions and/or concerns that the subject/legal representative may have and, if there is continued interest, will secure written informed consent from the subject's legal representative and assent from the subject for participation in the study. Written informed consent and any locally required authorization (eg, European Union [EU] Data Privacy Directive authorization), and written informed assent will be obtained prior to conducting any protocol-specific procedures, including screening evaluations or medication washouts. See Section 10.3 for additional details concerning informed consent.

4.2.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1) Age 12-17 years (inclusive) at both screening and Day 1

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

3) Physician diagnosed asthma for a minimum of 6 months prior to screening

4) Physician prescribed daily use of asthma controller medication as described at Steps 2-5 of GINA guidelines (GINA, 2010). The asthma controller regimen should have been stable for ≥ 3 months prior to screening and should not be expected to change during the course of the study. (Swapping between equivalent doses within the same class of asthma controller medication is permitted; eg, ICS.)

5) Prebronchodilator FEV_1 of ≥ 70% of predicted normal value at screening

6) A postbronchodilator increase in FEV_1 ≥ 12% and ≥ 200 mL at screening

7) Weight ≥ 30kg at both screening and Day 1

8) Body mass index (BMI) for age at both screening and Day 1 that is between fifth and 95th percentile (Centers for Disease Control Growth Charts, Appendix 5)

9) Able to comply with the requirements of the protocol

10) Females of childbearing potential who are sexually active with a nonsterilized male partner must use highly effective contraception from screening, and must agree to continue using such precautions through Day 57 of the study; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

    - Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy)
    - 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. Highly effective methods of contraception are described in Table 4.2.1-1 and those used during this study should be licensed for use in the relevant age group.

11) Nonsterilized males who are sexually active with a female partner of child-bearing potential must use a highly effective method of contraception (see Table 4.2.1-1) from Day 1 through Day 57. Cessation of birth control after this point should be discussed with a responsible physician.

Table 4.2.1-1 Highly Effective Methods of Contraception

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

[a] This is also considered a hormonal method.

4.2.2 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) Employees of the clinical study site or any other individuals involved with the conduct of the study, or immediate family members of such individuals

3) Pregnant or breastfeeding women

4) Individuals who are legally institutionalized

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

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

7) Receipt of any excluded concomitant medication as listed in Section 4.6.2 within 14 days (or 5-half lives, whichever is longer) of screening

8) History of a deterioration in asthma that required a burst of systemic corticosteroids within 3 months of screening, up to and including Day 1

9) History of hospitalization (overnight admission) for asthma during the 6 months prior to screening

10) History of intubation for the management of a deterioration in asthma

11) History of allergy or reaction to any component of the investigational product formulation or history of anaphylaxis following any biologic therapy

12) Current tobacco smoking or cessation of smoking for ≤ 3 months prior to screening

13) Any active medical condition other than asthma, that in the opinion of the investigator and/or medical monitor may compromise the safety of the subject in the study or interfere with evaluation of the investigational product or reduce the subject's ability

to participate in the study (subjects with atopic skin conditions and allergic rhinitis are permitted)

14) History of any known primary immunodeficiency disorder excluding asymptomatic selective immunoglobulin A

15) Clinical characteristics (eg, daytime symptoms, nocturnal symptoms, limitations of activities, need for reliever treatment and lung function PEF/FEV_1) at either screening or Day 1 that are consistent with uncontrolled asthma as described in GINA guideline (GINA, 2010; Appendix 2)

16) History of a clinically significant infection (eg, requiring antibiotics or antiviral medications) from 30 days prior to screening, up to and including Day 1

17) History of an untreated systemic helminth parasitic infection; diagnosis of a helminth parasitic infection within 6 months prior to screening; history of living with a person known to have had a helminth parasitic infection within 12 months prior to screening.

18) History of cancer

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

20) Evidence of active liver disease, including jaundice or aspartate transaminase (AST), alanine transaminase (ALT), or alkaline phosphatase greater than twice the upper limit (ULN) of normal

21) 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

22) 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

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

24) Any blood donation or significant loss of blood within 8 weeks of screening

25) 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. A positive test for drugs at Day 1

26) Receipt of allergen specific immunotherapy. No allergen specific immunotherapy should have been received within 30 days prior to screening

4.2.3 Withdrawal Criteria

Withdrawal of consent: If consent/assent is withdrawn, the subject will not receive further study observations or interventions.

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

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

4.2.4 Replacement of Subjects

Subjects who do not receive tralokinumab or do not complete the required evaluations through Day 8 may be replaced to maintain the stipulated number of subjects in each age group (10 subjects between 12-14 years old and 10 subjects will be between 15-17 years old. It is anticipated that a minimum of 8 subjects in each group are required to allow the estimation of PK parameters with adequate precision to achieve the objectives of the study.

4.3 Treatment Assignment

An IXRS will be used to assign investigational product kit numbers and to ensure equal distribution between age groups; 10 subjects will be between 12-14 years old and 10 subjects will be between 15-17 years old. A subject is considered entered into the study when the investigator or designee notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of investigational product kit numbers to the subject.

Each subject who meets the eligibility criteria will be assigned open-label investigational product.

The procedure for using IXRS is as follows:

- The investigator or designee confirms that written informed consent and subject assent has been obtained and that the subject has met all eligibility criteria.

- The investigator or designee calls or logs onto the IXRS and provides the SID and subject's baseline characteristic(s) used to verify that it is the same subject.
- The IXRS assigns an investigational product kit number to the subject.
- Confirmation of this information is sent to the investigational product manager at the site who dispenses the investigational product member to the team member who will administer investigational product to the subject, and records the appropriate information in the pharmacy record and investigational product accountability log.

Investigational product should be administered on the same day the investigational product is dispensed. If there is a delay in the administration of investigational product such that it will not be administered within the specific timeframe, the monitor should be notified *immediately*

4.4 Blinding

This study is not blinded.

4.5 Study Medications

4.5.1 Investigational Products

MedImmune will provide the investigators with investigational product (Table 4.5.1-1) using designated distribution centers. The sponsor will provide the investigator(s) with adequate stock quantities of investigational product.

Table 4.5.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Tralokinumab (CAT-354)	MedImmune	Formulated at a nominal concentration of 150 mg/mL [redacted].

Excipients are [redacted]

Labels 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.

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

4.5.1.1 Investigational Product 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 (refer to the written instructions provided by MedImmune or its designee for contact information and specific shipping instructions).

4.5.1.2 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.

Product defects may be related to component, product, or packaging and labeling issues. The list below includes, but is not limited to, descriptions of product complaints that should be reported.

- **Component Issue:** Defect in container or dosing mechanism of the investigational product. The component defect may be damaged, missing, or broken. Component examples include vials, stoppers, caps, spray barrels, spray nozzles, or plungers.
- **Product Issue:** Defect in the product itself. The product appearance has visual imperfections such as foreign particles, crystallization, discoloration, turbidity, insufficient volume, or anything that does not apply to the product description.
- **Packaging/Labeling Issue:** Defect in the packaging or labeling of the product. The packaging or labeling defects may be damaged or unreadable, or the label may be missing.

When reporting a product complaint, site staff must be prepared to provide the following information:

1) Customer information: reporter name, address, contact number, and date of complaint

2) Product information: product name, packaging kit number or lot number, expiry date, and clinical protocol number

3) Complaint information: complaint issue category and description

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com

[redacted]

Mail: MedImmune, LLC
Attn: Product Complaint Department
One MedImmune Way,
Gaithersburg, MD USA 20878

4.5.2 Other Study Medications

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

4.5.2.1 Background Medication

Subjects in this study will continue to receive asthma controller medications consistent with those described at Steps 2-5 of GINA guidelines (GINA, 2010) as prescribed by their physician. The asthma controller regimen should have been stable for ≥ 3 months prior to screening and should not be expected to change during the course of the study. If however the investigator considers a permanent change to the asthma controller regimen to be necessary, where possible the change should be discussed in advance with the sponsor's medical monitor, the subject may remain in the study, and the change must be recorded.

Theophylline, omalizumab, intramuscular corticosteroids and oral corticosteroids (OCS) > 10 mg/day prednisone (or equivalent) are not permitted in this study.

4.5.2.2 Rescue Medication

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

Subjects are expected to use inhaled SABA or an inhaled short-acting anticholinergic as a first-line treatment. If asthma symptoms do not resolve, subjects should contact the investigator (or their healthcare provider) who will manage the subject according to their

clinical judgement. Additional outpatient treatment may be required, eg, short-term courses of additional asthma controller medications, an OCS burst or, in the event of a marked deterioration, hospitalization/emergency room treatment may be necessary.

All treatments administered should be recorded.

4.5.3 Treatment Regimen

All 20 subjects will receive a single SC 300 mg dose of tralokinumab on Day 1. Investigational product (tralokinumab) will be administered as 2 SC injections of 1 mL.

4.5.4 Treatment Administration

The day of dosing is considered Day 1.

The investigational product will be administered by SC injection into the tissue of the anterior thigh. Two injections (150 mg per injection) are required in order to administer tralokinumab at the required dose of 300 mg; therefore, one injection of 150 mg should be given into the anterior aspect of one thigh immediately followed by a second injection of 150 mg into the anterior aspect of the contralateral thigh.

The investigational product will be administered via a 27-gauge 1/2-inch needle. The person administering the dose will wipe the skin surface of the thigh with alcohol and allow to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be inserted at a 90-degree angle approximately halfway into the SC tissue. The investigational product will be slowly injected (at least 5-second duration is recommended) into the SC tissue using gentle pressure. The area should not be massaged after injection.

4.5.5 Monitoring of Dose Administration

Vital signs (blood pressure, temperature, pulse rate, and respiration rate) will be obtained before investigational product administration. After investigational product administration, subjects will be monitored for immediate drug reactions; vital signs will be taken at 15, 30, 45 minutes, and 1, 4, and 8 hours after dosing. Discharge from site on Day 1 will be determined by the investigator and will be a minimum of 8 hours after dosing.

As with any antibody, allergic reactions to dose administration are possible. The World Health Organization has categorized anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic [IgE-mediated and non-IgE-mediated (eg, IgG and immune complex mediated) and nonimmunologic (Johansson et al, 2004). The clinical criteria for defining anaphylaxis for this study are listed in Appendix 3. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Appendix 4. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognize and treat anaphylaxis according to local guidelines.

4.5.6 Treatment Compliance

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

4.6 Concomitant Medications

4.6.1 Permitted Concomitant Medications

In addition to the background asthma and rescue medications described in Section 4.5.2.1 and Section 4.5.2.2 respectively, the following concomitant medications related to asthma/allergy treatment are permitted from screening (Day -14) through Day 57:

- Mucolytics and expectorants not containing bronchodilators
- Topical, nasal, and/or ocular formulations of corticosteroids or cromones
- Topical or oral antihistamines
- Topical dermatological preparation
- Inactivated vaccines

Hormonal contraceptives are permitted.

Subjects may receive short-term medications as supportive care or to treat AEs as deemed necessary by the investigator or the subject's physician.

All concomitant medications given to the subject from screening will be recorded.

4.6.2 Excluded Concomitant Medications

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

During the study, the use of regular concomitant medications (except those described in Sections 4.5.2.1, 4.5.2.2, and 4.6.1) and including over the counter drugs, herbal supplements, 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 during the study

- Immunosuppressive medication (eg, methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine, OCS > 10 mg/day prednisone (or equivalent), intramuscular long-acting depot corticosteroid)
- Oral corticosteroid burst or short-acting systemic corticosteroid for reasons other than acute asthma exacerbation
- Theophylline
- Tiotropium bromide
- Investigational agents
- Marketed biologics including omalizumab
- Immunoglobulin or blood products
- Use of any oral or ophthalmic β-adrenergic antagonist eg, propranolol
- Live attenuated vaccines

4.7 Subject Completion

An individual subject will be considered to have completed the study if the subject was followed up through the end of the study as defined in Section 4.8.

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

4.8 End of the Study

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

5 Study Procedures

5.1 Schedule of Study Procedures

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

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

A schedule of study procedures is presented in Table 5.1-1, followed by a description of each visit. A description of the study procedures is included in Section 5.2.

Table 5.1-1 Schedule of Study Procedures

Study Period	Consent	Consent/ Screening	Treatment Visit (Day 1) and Follow Up Period									
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Procedure / Study Day	**V2 -30 days**	**Day -14 to -1**	**Day 1**	**Day 2**	**Day 4**	**Day 6**	**Day 8**	**Day 10**	**Day 15**	**Day 22**	**Day 36**	**Day 57**
Written informed consent and assent	X											
Assignment of SID number		X										
Verify eligibility criteria		X	X									
Demography		X										
Medical and asthma history		X										
Physical examination		X	X						X			X
Weight		X	X									X
Height		X	X									X
Assessment of 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
12-Lead ECG		X										X
Spirometry (prebronchodilator at all visits, postbronchodilator in addition only at V2)		X	X				X			X		X
Serum chemistry		X	X				X		X		X	X
Hematology		X	X				X		X		X	X
Urinalysis		X	X				X		X		X	X

[redacted]

Table 5.1-1 Schedule of Study Procedures

Study Period	Consent	Consent/ Screening	Treatment Visit (Day 1) and Follow Up Period									
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Procedure / Study Day	**V2 -30 days**	**Day -14 to -1**	**Day 1**	**Day 2**	**Day 4**	**Day 6**	**Day 8**	**Day 10**	**Day 15**	**Day 22**	**Day 36**	**Day 57**
Pregnancy test (serum βHCG)		X										
Pregnancy test (urine βHCG)			X									X
Urine drug screen			X									
Virology: HBsAG, HCAb; HIV-1, HIV-2		X										
Pharmacokinetics blood sample			X	X	X	X	X	X	X	X	X	X
Immunogenicity blood sample			X									X
Investigational product administration			**X**									

AE = adverse event; HBsAG = hepatitis B surface antigen; HCAb = hepatitis C antibody; HIV = human immunodeficiency virus; ECG = electrocardiogram; βHCG = beta-human chorionic gonadotrophin; SAE - serious adverse event; SID = subject identification;

[redacted]

5.1.1 Screening

All screening procedures must be performed within 14 days before dosing (Day -14 to Day -1), unless otherwise specified. The screening evaluations may be carried out over more than one visit and the results of all laboratory investigations must be available prior to Day 1. Written informed consent and assent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations.

Subjects should attend the clinic to obtain informed consent from the legal representative and informed assent from the subject and all appropriate privacy documentation in accordance with local regulations. If the screening assessments are initiated at Visit 1 (consent visit); ie, Visit 1 and 2 assessments are undertaken at the same visit, they must be completed within 14 days. If the screening assessments are not initiated at Visit 1, the subject should return to the clinic within 30 days of their consent visit and must complete their screening assessments within 14 days of Visit 3 (the dosing visit).

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.

5.1.1.1 Days -14 (-30 days): Consent (Visit 1)

1) Obtain written informed consent and assent and appropriate privacy act document authorization

5.1.1.2 Days -14 to -1: Screening (Visit 2)

1) Assign an SID number
2) Verify eligibility criteria
3) Collect demographic information
4) Perform medical and asthma history
5) Perform physical examination
6) Measure weight and height
7) Perform 12-lead ECG
8) Measure vital signs
9) Spirometry pre and postbronchodilator

10) Collect blood for screening samples
    - Serum chemistry
    - Hematology
    - Virology: HIV-1, HIV-2, hepatitis B surface antigen, and hepatitis C antibody status
    - Beta-human chorionic gonadotrophin (βHCG) pregnancy test
11) Collect urine for screening sample
12) Assess for AEs and SAEs
13) Record concomitant medications

5.1.2 Treatment Period

5.1.2.1 Day 1: Dosing (Visit 3)

1) Verify eligibility criteria and enroll the subject
2) Perform physical examination (if applicable, record new findings as AEs or SAEs)
3) Measure weight and height
4) Assess for AEs and SAEs
5) Update concomitant medications
6) Spirometry prebronchodilator
7) Collect blood for baseline samples
    - Serum chemistry
    - Hematology
    - PK analysis
    - IM analysis
8) Collect urine for pregnancy test and drug screen; ensure result is negative.
9) Take vital signs before administration of investigational product
10) Administer investigational product
11) Collect blood for postdose PK samples at 3 (± 30 minutes) and 8 (± 30 minutes) hours postdose
12) Take vital signs (blood pressure and pulse rate) at 15, 30, 45 minutes, and 1, 4, and 8 hours postdose

Subjects will remain at the clinic for a minimum of 8 hours postdose.

5.1.2.2 Day 2: Follow-up after Dosing (Visit 4)

1) Measure vital signs
2) Update concomitant medications
3) Assess for AEs and SAEs
4) Collect blood for postdose PK sample (24 hours ± 30 minutes postdose)

5.1.2.3 Day 4: Follow-up after Dosing (Visit 5)

1) Update concomitant medications
2) Assess for AEs and SAEs
3) Collect blood for postdose PK sample

5.1.2.4 Day 6: Follow-up after Dosing (Visit 6)

1) Update concomitant medications
2) Assess for AEs and SAEs
3) Collect blood for postdose PK sample

5.1.2.5 Day 8 ± 1 day: Follow-up after Dosing (Visit 7)

1) Measure vital signs
2) Spirometry prebronchodilator
3) Collect blood for:
    - Serum chemistry
    - Hematology
    - Postdose PK sample
4) Collect urine for urinalysis
5) Update concomitant medications
6) Assess for AEs and SAEs

5.1.2.6 Day 10 ± 1 day: Follow-up after Dosing (Visit 8)

Same as Day 4 (Visit 5).

5.1.2.7 Day 15 ± 1 day: Follow-up after Dosing (Visit 9)

1) Perform physical examination

2) Measure vital signs
3) Collect blood for:
   - Serum chemistry
   - Hematology
   - Postdose PK sample
4) Collect urine for urinalysis
5) Update concomitant medications
6) Assess for AEs and SAEs

5.1.2.8 Day 22 ± 2 days: Follow-up after Dosing (Visit 10)

1) Spirometry prebronchodilator
2) Update concomitant medications
3) Assess for AEs and SAEs
4) Collect blood for postdose PK sample

5.1.2.9 Day 36 ± 2 days: Follow-up after Dosing (Visit 11)

1) Collect blood for:
   - Serum chemistry
   - Hematology
   - Postdose PK sample
2) Collect urine for urinalysis
3) Update concomitant medications
4) Assess for AEs and SAEs

5.1.3 Day 57 ± 2 days: End of Study Visit (Visit 12)

1) Perform physical examination
2) Measure weight and height
3) Perform vital signs
4) Perform 12-lead ECG
5) Spirometry prebronchodilator
6) Collect blood for:
   - Serum chemistry

- Hematology
- Postdose PK sample
- Postdose IM sample

7) Collect urine for urinalysis and βHCG pregnancy test

8) Update concomitant medication

9) Assess for AEs and SAEs

5.2 Description of Study Procedures

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

5.2.1 Medical and Asthma History

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

The asthma history questionnaire, also completed as part of the screening evaluations, includes questions related to the subject's asthma history, duration of asthma, and asthma medications.

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

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

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

5.2.2.1 Vital Signs

Vital signs (blood pressure, temperature, pulse rate, and respiration rate) will be obtained at all visits. On Day 1 vital signs will be obtained before investigational product administration. After investigational product administration, subjects will be monitored for immediate drug reactions; vital signs will be taken at 15, 30, 45 minutes, and 1, 4, and 8 hours after dosing. Discharge from site will be determined by the investigator.

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

5.2.2.2 Electrocardiogram

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

5.2.3 Spirometry

Spirometry will be performed by the investigator or qualified designee on equipment provided by a central vendor according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Miller et al, 2005). Prebronchodilator FEV_1 and FVC will be captured at all visits, postbronchodilator FEV_1 will only be captured at screening.

Spirometry testing must be performed in the morning between 6:00 and 11:00 AM according to the schedule of study procedures. At Day 1, spirometry testing will be performed before administration of tralokinumab.

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

Subjects will be required to refrain from strenuous exercise for 30 minutes prior to spirometry testing and to withhold the following medications or food prior to spirometry testing (Table 5.2.3-1). If a subject has taken these medications prior to a pre-arranged site visit, they should contact the site to reschedule their assessment visit.

Table 5.2.3-1 Prohibited Medication or Food and Minimum Time Intervals Prior to Spirometry Testing

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

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

Subjects should be sitting during spirometry. Nose clips will be used for clinic spirometry.

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

A postbronchodilator increase in $FEV_1 \geq 12\%$ and ≥ 200 mL at screening is an entry requirement. If this increase is not observed at screening (eg, if medications or food have not been optimally withheld prior to spirometry testing) the subject may undergo repeat reversibility testing on one occasion prior to Day 1 at the discretion of the investigator.

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

5.2.3.1 Pre- and Post-bronchodilator FEV1 Measurements Including Reversibility Calculations

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

1) Prebronchodilator FEV_1 measurement will be assessed as described above (Section 5.2.3).
2) After a gentle and incomplete expiration, a dose of 100 µg of salbutamol (or equivalent short acting bronchodilator) will be inhaled in one breath to total lung capacity from a spacer device.
3) Breath is then held for 5-10 seconds before the subject exhales. Four separate doses of 100 µg of salbutamol are delivered at 30 second intervals.
4) Wait 15-30 minutes (30 minutes if a short-acting anticholinergic agent is used).
5) Postbronchodilator FEV_1 measurement will be assessed and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded. The maximum FEV_1 of the 2 best efforts will be used for the analysis.

Total doses of less than 400 µg of salbutamol or equivalent may be used for the reversibility assessment at the discretion of the investigator if there are concerns about side effects (eg, heart rate or tremor).

Reversibility is calculated as follows:

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

5.2.4 Clinical Laboratory Tests

Clinical laboratory safety tests including serum pregnancy tests will be performed in a central clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal laboratory results should be repeated as soon as possible (preferably within 24-48 hours). These repeat tests may either be performed by the central clinical laboratory or by a laboratory local to the site as clinically indicated.

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

Serum Chemistry

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

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
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)

Urinalysis

- Nitrites (dipstick)
- Protein (dipstick)
- Glucose (dipstick)
- Ketones (dipstick)
- Urine drug screen (Visit 3)
- Blood (dipstick)
- Bilirubin (dipstick)
- Urine microscopy and urine casts (as required)
- Urine culture (as required)

Pregnancy Test (females of childbearing potential only)

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

Other Safety Tests

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

5.2.5 Pharmacokinetic Evaluation and Methods

For PK analyses, it is important that the time of each SC injection is recorded for each subject. On Day 1 serum will be collected immediately prior to dosing, then at 3

(± 30 minutes), 8 (± 30 minutes), and 24 (± 30 minutes) hours post dose, and on Days 4, 6, 8, 15, 22, 36, and 57. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to sites.

5.2.6 Immunogenicity Evaluation and Methods

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

5.2.7 Estimate of Volume of Blood to Be Collected

The estimated blood volumes by visit are presented in Table 5.2.7-1.

Table 5.2.7-1 Estimated Blood Volume

Study Day	Visit Number	Blood Volume (mL)
Days -14 to -1	2	7.0
1	3	19.0
2	4	3.5
4	5	3.5
6	6	3.5
8	7	10.5
10	8	3.5
15	9	10.5
22	10	3.5
36	11	10.5
57	12	12.0
Total blood volume		87.0

6 Assessment of Safety

6.1 Safety Parameters

6.1.1 Adverse Events

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

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

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

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

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

6.1.2 Serious Adverse Events

An SAE is any AE that:

- Results in death

- Is immediately life-threatening

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

- Requires inpatient hospitalization or prolongation of existing hospitalization

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

- Results in persistent or significant disability/incapacity

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

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

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

6.1.3 Other Events of Special Interest

6.1.3.1 Hepatic Function Abnormality

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN **and concurrent** increase in bilirubin to greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (eg, cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

6.2 Assessment of Safety Parameters

6.2.1 Assessment of Severity

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

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

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

6.2.2 Assessment of Relationship

6.2.2.1 Relationship to Investigational Product

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

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

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

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

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

6.2.2.2 Relationship to Protocol Procedures

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

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

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

6.3 Recording of Safety Parameters

6.3.1 Recording of Adverse Events and Serious Adverse Events

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

6.3.2 Recording of Other Events of Special Interest

Hepatic Function Abnormality

Events of hepatic function abnormality (as defined in Section 6.1.3.1) should be recorded according to the definitions of AE and SAE (Section 6.1.1 and Section 6.1.2, respectively):

- If an event of hepatic function abnormality is considered to be related to a pre-existing condition and does not represent a worsening of this condition and/or is considered to be within the range of normal physiological fluctuation for the subject, the event does not meet the definition of an AE and does not need to be recorded as such.
- If a definitive diagnosis for an underlying condition unrelated to the investigational product is established for an event of hepatic function abnormality, the diagnosis should be recorded as an AE/SAE per Section 6.3.1.
- If no definitive diagnosis is determined for an event of hepatic function abnormality, the term "hepatic function abnormal" should be used to report the AE/SAE per Section 6.3.1.

6.4 Reporting Requirements for Safety Parameters

6.4.1 Study Reporting Period and Follow-up for Adverse Events

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

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

6.4.2 Reporting of Serious Adverse Events

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

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

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

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

6.4.2.2 Notifying the Sponsor of Serious Adverse Events

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

MedImmune contact information:

Patient Safety
MedImmune
[redacted]

The sponsor is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH Guidelines and/or local regulatory requirements (see Section 6.4.2.3). The sponsor may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the sponsor as soon as it becomes available.

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

6.4.2.3 Safety Reporting to Investigators, Independent Ethics Committees, and Regulatory Authorities

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

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

6.4.3 Other Events Requiring Immediate Reporting

6.4.3.1 Overdose

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

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

6.4.3.2 Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 6.1.3) in a study subject, with or without associated clinical manifestations, 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 (see Section 6.4.2.2 for contact information), unless a definitive underlying diagnosis for the abnormality (eg, cholelithiasis and bile duct obstruction) that is unrelated to investigational product has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor. If the etiology of the event remains unconfirmed and/or is considered related to investigational product (see Section 6.2.2.1), a prompt cumulative review of safety data and the circumstances of the event in question will be conducted and assessed by the MedImmune SMC (see Section 6.5) to determine whether continued dosing of study subjects should be interrupted, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the SMC is required for resumption of subject dosing or study randomization in the event that the study is interrupted. Where applicable, regulatory authorities and IECs will be notified of any actions taken with the study.

6.4.3.3 Pregnancy

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

After obtaining the subject's consent, the pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to MedImmune Patient Safety after outcome. If the partner of a male subject becomes pregnant, her consent will be obtained to follow-up the pregnancy until outcome.

6.4.3.4 Events Meeting Study Stopping Criteria

Events that meet any of the study stopping criteria (Section 3.3), with or without associated AEs or SAEs, are required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 6.4.2.2 for

contact information). The occurrence of these events does not automatically make an AE serious, but if the consequences of the event are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 6.3.1 and Section 6.4.2).

6.5 Safety Management During the Study

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

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

7 Statistical Considerations

7.1 General Considerations

Data will be provided in data listings sorted by subject number. Tabular summaries will be presented. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Confidence intervals (CIs) will be two-sided, unless otherwise stated. Details of endpoint analyses will be described in the statistical analysis plan.

7.2 Analysis Populations

The PK population includes all subjects who receive the investigational product and who have at least one detectable post dosing tralokinumab serum concentration

The safety population includes all subjects who receive any investigational product

7.3 Endpoints

7.3.1 Primary Endpoint

Individual tralokinumab serum concentrations will be tabulated along with descriptive statistics. The following PK parameters will be estimated by noncompartmental analysis: areas under the time-concentration curves from zero to infinity and to last observation ($AUC_{(0\text{-infinity})}$; $AUC_{(0\text{-t})}$); dose-normalized $AUC_{(0\text{-infinity})}$ ($AUC_{(0\text{-infinity})}$/D); C_{max}; dose-normalized C_{max} (C_{max}/D); time to C_{max} (T_{max}); terminal-phase elimination half-life ($t_{1/2}$); apparent clearance (CL/F); steady-state volume of distribution (Vss/F).

Descriptive statistics for serum tralokinumab concentration data will be provided and will include N, geometric mean, arithmetic mean, standard deviation (SD), percent coefficient of variation, median, minimum, and maximum. Plots of the mean and individual serum concentrations over time of tralokinumab will be provided. Using the serum concentrations of tralokinumab, the pharmacokinetics of tralokinumab will be analyzed using the non-compartmental method as implemented in WinNonlin® Professional version 5.1 or higher.

The PK data gathered in this study will be added to a population PK model to assess any PK differences between adolescents and adults and guide dosing for future studies that include adolescents.

7.3.2 Secondary Endpoints

Safety and tolerability of a single-dose SC injection of tralokinumab will be assessed through the incidence of treatment-emergent AEs, and the assessment of vital signs, physical examinations, laboratory parameters, and ECG.

Immunogenicity of tralokinumab will be evaluated. The incidence rate of positive serum antibodies to tralokinumab will be reported.

7.3.3 Exploratory Endpoints

The effect of tralokinumab on pulmonary function as measured by pre bronchodilator FEV_1 will be assessed. Change from baseline in the mean values and percent change from baseline at various time points will be summarized using descriptive statistics.

7.4 Interim Analysis

No interim analysis is planned.

7.5 Sample Size

The number of subjects has been based on the desire to obtain adequate PK and safety data while exposing as few subjects as possible to tralokinumab and procedures. A total of 20 subjects are considered sufficient to provide adequate information and to ensure that the study includes subjects across the adolescent age range, 10 subjects will be 12-14 years old and 10 subjects will be 15-17 years old.

8 Direct Access to Source Documents

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

9 Quality Control and Quality Assurance

9.1 Data Collection

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

Subject demographics may be collected, as available, for all subjects who provide written informed consent. For subjects who provide informed consent and were not entered into the study, the reason the subject was not entered, ie, did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (eg, lost to follow-up, consent withdrawn), may also be collected.

9.2 Study Monitoring

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

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

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

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

9.3 Audit and Inspection of the Study

During and after the study, the sponsor or its representative may conduct audits of any data and any facility participating in the study. The investigator and institutions involved in the study will permit such study-related audits and provide direct access to all study records and facilities. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the sponsor or its designated monitors, auditors, or regulatory agency representatives. The investigator agrees to participate in audits conducted at a convenient time in a reasonable manner.

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

10 Ethics

10.1 Regulatory Considerations

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

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

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

10.2 Independent Ethics Committee

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

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

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

The IEC must be informed by the investigator of informed assent/consent form changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study (as applicable according to local regulations); new information that may affect adversely the safety of the subjects or the conduct of the

study; an annual update and/or request for re-approval; and when the study has been completed.

10.3 Informed Consent

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

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

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

10.4 Withdrawal of Consent for Continued Study Participation

Data and Samples Obtained for the Main Study

Study data are protected by the use of a subject identification number, which is a number specific to the subject. The investigator is in control of the information that is needed to

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

Samples Obtained for Future Research

Samples obtained for future research will be labeled with a sample identification number but will not be labeled with personal identifiers such as the subject's name. A file linking this sample identification number with the subject identification number will be kept in a secure place at the sponsor with restricted access. If the subject withdraws consent for participating in the future research, this link will allow the sponsor to locate the subject's sample and destroy it. The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

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

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

11 Data Handling and Record Keeping

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a subject's identification

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

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

12 Financing and Insurance

Financing and insurance are addressed in the individual site contracts.

13 Publication Policy

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

14 References

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15 Summary of Protocol Amendments and Administrative Changes to the Protocol

Not applicable, this is the original protocol

Appendix 1 Signatures

Sponsor Signature(s)

A Phase 1, Open-label Study to Evaluate the Safety and Pharmacokinetics of Tralokinumab in Adolescents with Asthma

I agree to the terms of this protocol.

Signature and date: _____

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Sponsor Signature(s)

A Phase 1, Open-label Study to Evaluate the Safety and Pharmacokinetics of Tralokinumab in Adolescents with Asthma

I agree to the terms of this protocol.

Signature and date: _____

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Sponsor Signature(s)

A Phase 1, Open-label Study to Evaluate the Safety and Pharmacokinetics of Tralokinumab in Adolescents with Asthma

I agree to the terms of this protocol.

Signature and date: _____

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Signature of Principal Investigator

A Phase 1, Open-label Study to Evaluate the Safety and Pharmacokinetics of Tralokinumab in Adolescents with Asthma

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 (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 IEC, and must be approved by the 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 IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available) _____

Signature of Coordinating Investigator

A Phase 1, Open-label Study to Evaluate the Safety and Pharmacokinetics of Tralokinumab in Adolescents with Asthma

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 (IEC).

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Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available or applicable) _____

Appendix 2 Global Initiative for Asthma: Approach to Asthma Control and Levels of Asthma Control

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

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

LABA - long-acting β_2-agonist

*ICS - inhaled glucocorticosteroids

** - Receptor antagonist or synthesis inhibitors

***Preferred controller options are in bold

Adapted from GINA 2010

Levels of Asthma Control

Assessment of Current Clinical Control (Preferably over 4 weeks)			
Characteristic	**Controlled (All of the Following)**	**Partly Controlled (Any Measure Present)**	**Uncontrolled**
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma [a] [b]
Limitation of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF of FEV1) [c]	Normal	< 80% predicted or personal best (if known)	

FEV1 = forced expiratory flow in 1 second; PEF = peak expiratory flow

[a] Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate

[b] By definition, an exacerbation in any week makes that an uncontrolled asthma week

[c] Without administration of bronchodilator, lung function is not a reliable test for children 5 years and younger

Adapted from GINA 2010

Appendix 3 Clinical Criteria for Defining Anaphylaxis and Immune Complex Disease

Anaphylaxis

In adults, anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING

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

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

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

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

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

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

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

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

Immune Complex Disease

Immune complex disease or Hypersensitivity Type III is evoked by the deposition of antigen-antibody or antigen-antibody-complement complexes on cell surfaces, with subsequent involvement of breakdown products of complement, platelets, and polymorphonuclear leukocytes, and development of vasculitis; serum sickness and nephritis is common.

Appendix 4 Signs and Symptoms and Management of Acute Anaphylaxis

Signs and Symptoms of Acute Anaphylaxis

Anaphylaxis is an acute and potentially lethal multi-system allergic reaction in which some or all of the following signs and symptoms occur:

- Diffuse erythema
- Pruritus
- Urticaria and/or angioedema
- Bronchospasm
- Laryngeal edema
- Hypotension
- Cardiac arrhythmias
- Feeling of impending doom
- Unconsciousness
- Shock

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles
- Rhinorrhea
- Change in voice
- Metallic taste
- Nausea, vomiting, diarrhea, abdominal cramps and bloating
- Lightheadedness
- Headache
- Uterine cramps
- Generalized warmth

Management of Acute Anaphylaxis

I. Immediate intervention

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

b. Administer epinephrine intramuscularly every 5-15 minutes, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms such as respiratory distress, hypotension, shock and unconsciousness.

II. Possibly appropriate, subsequent measures depending on response to epinephrine

a. Place patient in recumbent position and elevate lower extremities.

b. Establish and maintain airway.

c. Administer oxygen.

d. Establish venous access.

e. Normal saline IV for fluid replacement.

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

a. Consider epinephrine infusion.

b. Consider H1 and H2 antihistamines.

c. Consider nebulized β2 agonist [eg, albuterol (salbutamol)] for bronchospasm resistant to epinephrine.

d. Consider systemic corticosteroids.

e. Consider vasopressor (e.g. dopamine).

f. Consider glucagon for patient taking b-blocker.

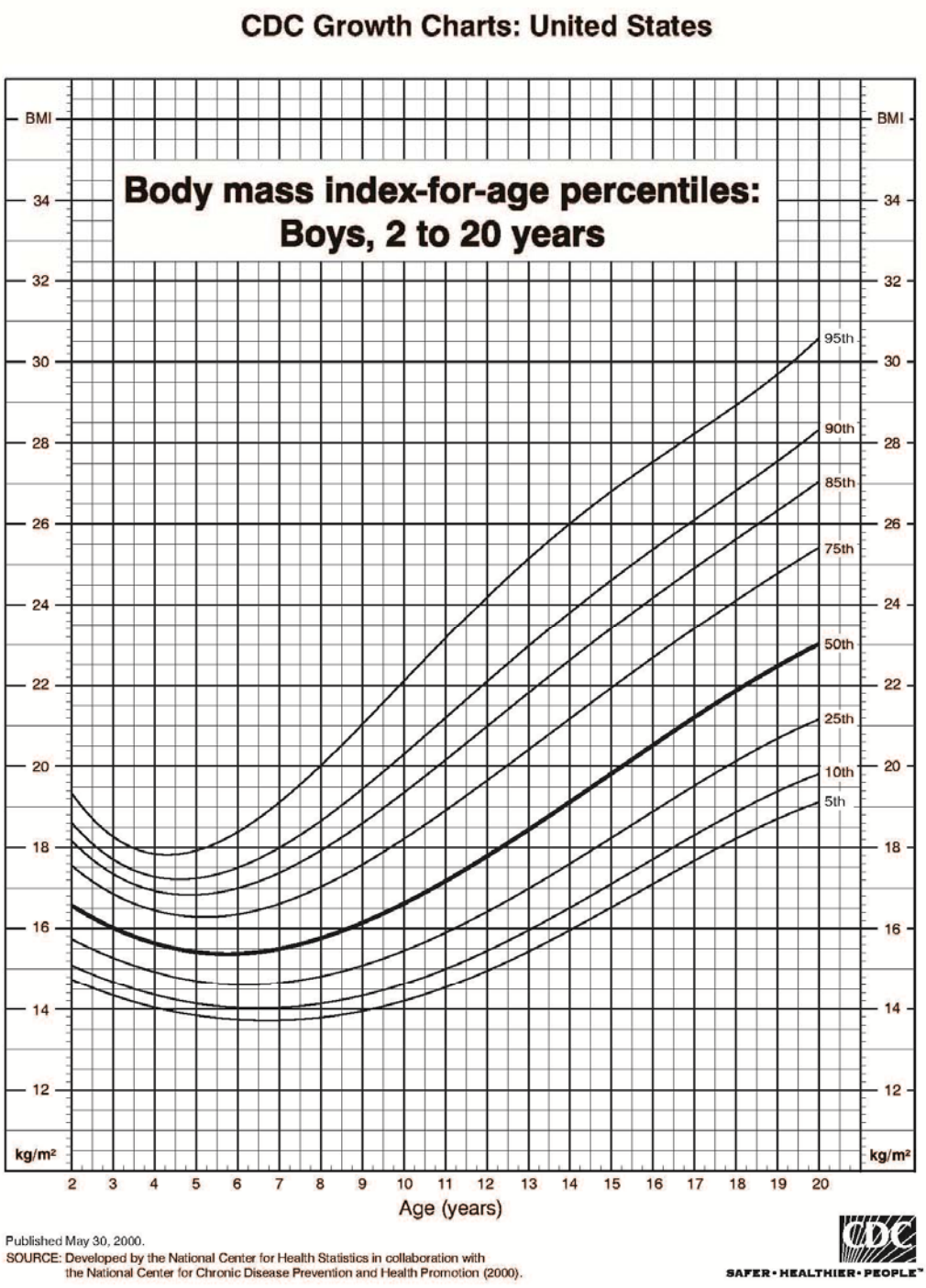
g. Consider atropine for symptomatic bradycardia.

h. Consider transportation to an emergency department or an intensive care facility.

i. For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary.

Adapted from: Kemp SF, Lockey RF, Simons FE; World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy. 2008; 63(8):1061-70.

Appendix 5 Centers for Disease Control Growth Charts



CDC Growth Charts: United States