A PHASE 1, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFECTS OF MEDI-563, A HUMANIZED ANTI-INTERLEUKIN-5 RECEPTOR ALPHA MONOCLONAL ANTIBODY, ON AIRWAY EOSINOPHILS IN ADULTS WITH ASTHMA

Study Agent: MEDI-563

MedImmune Protocol Number: MI-CP166

IND Number: IND 100,237

Manufacturer: MedImmune
[redacted]

Sponsor: MedImmune

Medical Monitor: [redacted]

Study Monitor: MedImmune
[redacted]

Principal Investigator Agreement:

I, the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with Good Clinical Practice, the ethical principles set forth in the Declaration of Helsinki and with the U.S. Code of Federal Regulations governing the protection of human subjects (21 CFR 50), Institutional Review Boards (21 CFR 56) and the obligations of clinical investigators (21 CFR 312).

Signature_____ Date_____

Printed Name_____

[redacted]

LIST OF ABBREVIATIONS

ACQ	Asthma Control Questionnaire
ADCC	Antibody-dependent cell cytotoxicity
AE	Adverse Event
AHR	Airway hyperresponsiveness
ALT	Alanine transaminase
AST	Aspartate transaminase
ATS	American Thoracic Society
AQLQ(S)	Asthma Quality of Life Questionnaire (Standardized version)
AUC	Area under the concentration-time curve
BAL	Bronchoalveolar lavage
βHCG	Beta human chorionic gonadotropin (pregnancy test)
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of federal regulations
CL	Systemic clearance
C_{max}	Maximum observed concentration
CPK	Creatine phosphokinase
CTMM	Clinical Trial Material Manager
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CXR	Chest X-ray
ECG	Electrocardiogram
ECP	Eosinophilic cationic protein
EDN	Eosinophilic derived neurotoxin
ELISA	Enzyme-linked immunosorbent assay
eNO	Exhaled nitric oxide
ER	Emergency room
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GGT	Gamma glutamyltransferase
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
$IgG_{1\kappa}$	Immunoglobulin G_1 kappa
IL	Interleukin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-6	Interleukin-6
IM	Immunogenicity
IND	Investigational new drug application
IRB	Institutional Review Board

IRE	Immediately Reportable Event
IV	Intravenous
IVIG	Intravenous immunoglobulin
IVRS	Interactive voice response system
Ke	Elimination rate constant
LDH	Lactate dehydrogenase
MAb	Monoclonal antibody
MEDI-563	Humanized $IgG_{1\kappa}$ monoclonal antibody derived from the murine, anti-human IL-5Rα MAb, MS705
NOAEL	No-observed-adverse-effect level
NK	Natural killer cells
PEFR	Peak expiratory flow rate
PID	Participant identification number
PK	Pharmacokinetics
PPB	Parts per billion
PPD	Mantoux purified protein derivative test for TB
PT	Prothrombin time
PTT	Partial thromboplastin time
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SMC	Safety monitoring committee
SOC	System organ class
TB	Tuberculosis
T_{max}	Time when the maximum concentration is observed
$t_{1/2}$	Elimination half-life
ULN	Upper limits of normal
USA	United States of America
WBC	White blood count

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STUDY ABSTRACT

TITLE:

A Phase 1, Double-Blind, Placebo-Controlled Study To Evaluate the Safety, Tolerability and Effects of MEDI-563, A Humanized Anti-Interleukin-5 Receptor Alpha Monoclonal Antibody, On Airway Eosinophils in Adults with Asthma

OBJECTIVES:

The primary objectives of this study are to:

1. Evaluate the safety and tolerability of MEDI-563 in adults with asthma; and
2. Evaluate the effects of MEDI-563 on eosinophil counts in airway mucosal biopsies 28 days after completion of dosing in adults with asthma.

The secondary objectives of this study are to:

1. Evaluate the pharmacokinetics (PK) of MEDI-563 in adults with asthma; and
2. Evaluate the immunogenicity (IM) of MEDI-563 in adults with asthma.

The exploratory objectives of this study are to:

1. Evaluate the effects of MEDI-563 on disease activity;
2. Evaluate the effects of MEDI-563 on inflammatory cells and proteins in mucosal biopsies, including eosinophils in mucosal biopsies;
3. Evaluate the effects of MEDI-563 on inflammatory cells and proteins in induced sputum;
4. Evaluate the effects of MEDI-563 on eosinophils and eosinophil precursors in bone marrow in adults with asthma;
5. Evaluate the effects of MEDI-563 on peripheral blood levels of eosinophil and basophil derived proteins and cytokines in adults with asthma;
6. Evaluate the effects of MEDI-563 on peripheral blood eosinophil and basophil counts;
7. Evaluate downstream effects of MEDI-563 on mRNA levels in whole blood, using microarray analyses; and
8. Explore single-nucleotide-polymorphisms and microsatellite or short tandem repeat analyses for genes associated with asthma in whole blood DNA, if such analyses are warranted based on other exploratory analyses in adults with asthma.

DESIGN:

This is a Phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and effects of single IV and multiple SC administration of MEDI-563 on airway eosinophils in adults with asthma who have ≥ 2.5% eosinophils in sputum. A total of up to 24 subjects are expected to be enrolled at approximately 10 investigative sites in the USA and Canada.

[redacted]

The first 12 subjects will be randomized in a 2:1 ratio to receive a single IV dose of MEDI-563 (1.0 mg/kg) or placebo (Cohort 1), with 8 subjects receiving MEDI-563 and 4 subjects receiving placebo. This cohort may be expanded by up to 3 additional subjects (for a maximum of 15 subjects) if eligible subjects are already in screening at the time 12 subjects have been randomized into the dose cohort. On Study Day 28, these subjects will undergo an airway biopsy. Decisions regarding whether to proceed with single-dose cohorts or multiple-dose cohorts were to be based on biopsy results as follows:

- If the airway biopsy results from subjects treated with MEDI-563 indicate a mean reduction in eosinophil count of ≥ 80% from baseline (Study Day 0), subsequent cohorts will receive reduced single IV doses of MEDI-563 or placebo.

- If the airway biopsy results from subjects treated with MEDI-563 indicate a mean reduction in eosinophil count of < 80% from baseline (Study Day 0), subsequent cohorts will receive multiple IV doses of MEDI-563 or placebo.

The decision tree above was removed to include the evaluation of multiple-dose SC administration (100 mg and 200 mg) instead of single or multiple-dose IV administration of MEDI-563 due to the development of the SC formulation of MEDI-563 and the intent to proceed with multiple-dose SC administration in the future.

A total of 13 subjects received a single IV dose of MEDI-563 (1.0 mg/kg) or placebo (Cohort 1) in this study under previous versions of the study protocol. Cohort 1 completed the study, and the data remain blinded per protocol.

A second group of 12 subjects (Cohort 2) will be randomized in a 1:1:1 ratio to receive 1 of 2 doses of MEDI-563 (100 mg or 200 mg) or placebo as an SC injection once every 4 weeks for 8 weeks (Study Day 0, Study Day 28, and Study Day 56). This cohort may be expanded by up to 3 additional subjects (for a maximum of 15 subjects) if eligible subjects are already in screening at the time 12 subjects have been randomized into the dose cohort.

Subjects will be screened for up to 14 days. Study drug administration will occur on Study Day 0 for Cohort 1 and on Study Days 0, 28, and 56 for Cohort 2. All subjects will be followed for at least 12 weeks after study drug administration (through Study Day 84 for Cohort 1 and through Study Day 140 for Cohort 2). Bronchoscopies with biopsies consisting of 4-6 subsegmental and segmental biopsies in each procedure will be performed at 2 time points during the study (screening and Study Day 28 for Cohort 1 or screening and Study Day 84 for Cohort 2). For Cohort 1 only, an additional optional bronchoscopy and biopsies may be performed on Study Day 84.

SUBJECT POPULATION:

The subjects in this study will be adults with asthma who have ≥ 2.5% eosinophils in sputum.

[redacted]

TREATMENT:

Subjects in Cohort 1 will receive either MEDI-563 (1.0 mg/kg) or placebo as an IV infusion, with 8 subjects receiving MEDI-563 and 4 subjects receiving placebo. This cohort may be expanded by up to 3 additional subjects (for a maximum of 15 subjects) if eligible subjects are already in screening at the time 12 subjects have been randomized into the dose cohort. All infusions must be administered with a 0.22 μm protein-sparing/low in-line filter, which will be supplied by the sponsor. All doses must be administered over at least 30 minutes.

Cohort	N	Treatment
1	12	1.0 mg/kg IV: MEDI-563 (N=8) / Placebo (N=4) on Study Day 0

Subjects in Cohort 2 will receive 1 of 2 doses of MEDI-563 (100 mg or 200 mg) or placebo as an SC injection once every 4 weeks on Study Days 0, 28, and 56. Four subjects will receive each MEDI-563 dose and 4 subjects will receive placebo. This cohort may be expanded by up to 3 additional subjects (for a maximum of 15 subjects) if eligible subjects are already in screening at the time 12 subjects have been randomized into the dose cohort. The study drug will be administered by injection into the SC tissue of the triceps muscle of the arm.

Cohort	N	Treatment
2	4	100 mg SC MEDI-563 on Study Days 0, 28, and 56
	4	200 mg SC MEDI-563 on Study Days 0, 28, and 56
	4	Placebo SC on Study Days 0, 28, and 56

SUBJECT EVALUATION AND FOLLOW-UP:

Subjects in Cohort 1 will be screened for up to 14 days, and then study drug administration will occur on Study Day 0, and subjects will be followed for at least 12 weeks after study drug administration. Bronchoscopies with biopsies consisting of 4-6 subsegmental and segmental biopsies in each procedure will be performed at least at 2 time points during the study (and Study Day 28) with an additional optional bronchoscopy and biopsies performed on Study Day 84. Safety and efficacy evaluations for subjects in Cohort 1, including assessment of adverse events (AEs) and serious adverse events (SAEs), will be performed from screening through at least End of Study/Study Termination (Study Day 84).

Subjects in Cohort 2 will be screened for up to 14 days, and then study drug administration will occur on Study Days 0, 28, and 56. Subjects will be followed for at least 12 weeks after study drug administration. Bronchoscopies with biopsies consisting of 4-6 subsegmental and segmental biopsies in each procedure will be performed at 2 time points during the study (screening and Study Day 84).

[redacted]

If, at the End of Study/Study Termination visit (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2), a subject's eosinophil count in peripheral blood is not at least 100 eosinophils/mm^3 OR the peripheral blood eosinophil count has not returned to at least 70% of the baseline value, the subject will return to the study site every other month until the subject's eosinophil count meets one of the criteria above.

ASSESSMENT OF ENDPOINTS:

The primary endpoints of this study are to evaluate the safety and tolerability of MEDI-563 and to evaluate the effect of MEDI-563 on airway mucosal eosinophils 28 days after completion of dosing in adults with asthma. Safety and tolerability will be assessed by summarizing AEs. The occurrence of AEs will be reported from the time the subject signs the informed consent through End of Study/Study Termination (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2). The occurrence of SAEs will be reported from the time the subject signs the informed consent through End of Study/Study Termination (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2), or until the long-term follow-up period is complete, if applicable. Other variables used for the safety assessments include serum chemistry, complete blood count (CBC) with differential and platelets, and urinalysis. These variables as well as their changes from baseline will be summarized descriptively. Percent change from baseline in eosinophil counts in the airway mucosa (Study Day 28 for Cohort 1 or Study Day 84 for Cohort 2) will be summarized by cohort and treatment group.

The secondary endpoints of this study are to evaluate the PK and IM of MEDI-563. Noncompartmetal pharmacokinetic parameters to be reported include but are not limited to, the maximum observed plasma concentration of MEDI-563 (C_{max}), area under the concentration-time curve (AUC), the terminal elimination half-life ($t_{1/2}$) and systemic clearance (CL) for Cohort 1, if the data allow. For Cohort 2, C_{max} and pre-dose trough (C_{min}) plasma concentrations will be summarized following each dose. Descriptive statistics of these noncompartmental parameters by dose cohort will also be provided. Immunogenicity will be evaluated by analyzing plasma samples for the detection of the presence of anti-MEDI-563 antibodies following MEDI-563 dosing. Immunogenicity results will be listed for each subject, and the percentage of subjects who developed detectable anti-MEDI-563 antibodies will be calculated and reported.

Exploratory endpoints include examining evidence of the clinical activity of MEDI-563. Spirometry endpoints will be evaluated using indicators including forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). Other changes in disease activity, such as peak morning flow, Asthma Control Questionnaire (ACQ), use of rescue β2 agonist medication, and Asthma Quality of Life Questionnaire (Standardized Version) [AQLQ(S)] will be evaluated in the MEDI-563 and placebo groups. Sputum inflammatory cells, number of bone marrow eosinophils and eosinophil precursors, serum levels of eosinophil- and basophil-derived proteins and inflammatory cytokines, cells in airway mucosal biopsies, downstream effects of MEDI-563 on mRNA levels in whole blood, and exploration of single-nucleotide-polymorphisms and microsatellite or short tandem repeat analyses in whole blood DNA. All these endpoints and corresponding change from baseline will be summarized by cohort and treatment group.

All endpoints will be summarized by cohort and treatment group.

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1 INTRODUCTION

1.1 Background

1.1.1 Overview of Asthma

Asthma is a syndrome characterized by airway inflammation, reversible variable airway obstruction, and airway hyperresponsiveness (AHR). Subjects with asthma may have chronic inflammation of the airways even when in clinical remission (van den Toorn et al, 2001). Progressive pathologic airway remodeling and scarring may result in partially reversible or irreversible airway obstruction (Pascual and Peters, 2005).

Asthma is a critical clinical and public health problem in the United States of America (USA) and the rest of the world. As of 2003, approximately 10.4% of people in the USA, or 30 million people, had a history of asthma sometime in their lifetime (Centers for Disease Control, 2003). Of this cohort, the prevalence of current asthma was 20 million. Estimates are that nearly half of all current asthmatics have moderate or severe asthma, with 31% having moderate persistent asthma and 16% having severe persistent asthma (Stoloff, 2000).

The National Heart, Lung, and Blood Institute has provided guidelines for the treatment of asthma. The major goals of asthma therapy are to prevent chronic asthma symptoms and asthma exacerbations during the day and night, as indicated by no sleep disruption, no missed work or school, and no or minimal need for emergency room (ER) visits or hospitalizations. Current therapies for asthma consist of long-term control medications and rescue medications for acute exacerbations. The most effective long-term control medications for asthma are those that reduce inflammation. Inhaled corticosteroids (ICS) are the most potent anti-inflammatory medication currently available for persistent asthma; long-term use of ICS may lead to adverse effects. Other long-term control medications include long-acting β2 agonists, theophylline, mast cell stabilizers, leukotriene modifiers, and combination therapies. Rescue medications are used to provide prompt treatment of acute airflow obstruction and its accompanying symptoms. These medications include primarily short-acting bronchodilators including short-acting β2 agonists and occasionally anticholinergics. Long-term use of long-acting and short-acting β2 agonists have been associated with increased mortality (Nelson et al, 2006; Anderson et al, 2005). There is a need for additional effective treatment for asthma to achieve optimal outcomes for subjects.

1.1.2 Role of Eosinophils in Asthma

Eosinophils are thought to play a critical role in the pathogenesis and severity of asthma. Reduction of eosinophils in sputum has been shown to be associated with better asthma control (Green et al, 2002) and increases in sputum eosinophilia are associated with exacerbations of both asthma and chronic obstructive pulmonary disease (COPD) (Scott and Wardlaw, 2006).

Interleukin-5 (IL-5) is a cytokine secreted predominantly by T-lymphocytes, mast cells, and eosinophils and is involved in regulating the differentiation, proliferation, and activation of eosinophils via the IL-5 receptor (IL-5R). The IL-5R is a heterodimer consisting of an α-chain and a β-chain. Monomeric IL-5Rα are low affinity receptors, while dimerization with the β-chain

produces a high affinity receptor (Tavernier et al, 1991). In the absence of IL-5 interaction with the α-chain, binding to the β-chain alone by the ligand does not occur.

Expression of the IL-5Rα chain is restricted largely to eosinophils, basophils, and some mast cells in humans (Toba et al, 1999; Dahl et al, 2004). The α-chain exclusively binds IL-5 and the intracellular portion of IL-5Rα is associated with Janus kinase 2, a protein tyrosine-kinase essential in IL-5 signal transduction (Ogata et al, 1998; Takaki et al, 1994).

Thus, IL-5Rα may be a good target for a therapeutic antibody in the management of asthma. Eosinophils, and perhaps basophils and some mast cells, can be preferentially targeted for antibody-dependent cell cytotoxicity (ADCC) through IL-5Rα, depleting cells thought to be key in disease pathogenesis and severity. In addition, blocking of IL-5Rα could provide benefit by neutralizing effects of IL-5. Previous clinical studies with an anti-IL5 monoclonal antibody (MAb) failed to show reductions in AHR or increases in forced expiratory volume in 1 second (FEV_1) and peak expiratory flow rate (PEFR). The anti-IL5 MAb was associated with incomplete depletion (mean 55%) of eosinophils in the airways, leading to the hypothesis that incomplete depletion of eosinophils in the airways explained lack of clinical effect (Flood-Page et al, 2003). The purpose of this study is to test whether a MAb that targets IL-5Rα, rather than IL-5, and is engineered to augment ADCC (MEDI-563) would provide near complete (more than 80%) reduction in airway eosinophils. This characteristic of MEDI-563 would provide the opportunity to test in future studies whether complete depletion of eosinophils in the airways is associated with therapeutic benefit in asthma.

1.2 Description of MEDI-563

MEDI-563 (formerly known as BIW-8405) is a recombinant, a-fucosylated, humanized MAb to the IL-5Rα. The MAb was humanized by replacing mouse for human constant regions of the $IgG_{1\kappa}$ isotype and is composed of 2 heavy chains (IgG1) and 2 light chains (kappa), with a molecular weight of approximately 150 kilodaltons. Fucose was removed from glycosylation to increase ADCC activity of MEDI-563.

1.3 Nonclinical Experience with MEDI-563

In vitro studies have shown that MEDI-563 binds to eosinophils through the IL-5Rα, and blocks the binding of the ligand, IL-5 to the receptor and activates effector cells for expression of ADCC activity causing the apoptosis of eosinophils. In addition, studies in a number of in vivo models (cynomolgus monkey) of peripheral eosinophilia and allergic asthma demonstrated that MEDI-563 would work in vivo as an anti-eosinophil therapeutic reagent. The close similarity between human and cynomolgus monkey tissue cross-reactivity profiles confirmed that the cynomolgus monkey was an appropriate animal species for study.

Toxicology studies were conducted in cynomolgus monkeys following intravenous (IV) and subcutaneous (SC) administration of MEDI-563. MEDI-563 was administered IV once every 3 weeks for 9 weeks (on Days 1, 22, 43, and 64) at dose levels of 0 (control), 0.1, 1.0, 10.0 and 30 mg/kg with an 18-day recovery period to evaluate reversibility of any MEDI-563 effects. A marked depletion of peripheral blood eosinophils was evident shortly after dose initiation at all

dose levels and persisted throughout the study. Decreased leukocyte levels which resulted from differential decreases in neutrophils were transiently seen in one high-dose (30.0 mg/kg) male and one high-dose female during the dosing period. The observed eosinophil depletion from peripheral blood was an anticipated pharmacological effect of the test article and no other signs of test article treatment were observed in any of the other in-life or post-mortem examinations and assessments of the study. In addition, depletion of eosinophil progenitors was evident in the bone marrow without affecting the neutrophil lineage. Under the conditions of the study, the no-observed-adverse-effect level (NOAEL) for MEDI-563 was ≤ 30.0 mg/kg; the neutrophil change noted in 2 of 10 animals treated in the 30.0 mg/kg group was mild and temporary.

When MEDI-563 (1, 10, or 30 mg/kg) was administered to cynomolgus monkeys as a SC injection every other week for 15 weeks (8 total doses), no adverse test article-related changes were identified, resulting in a NOAEL of at least 30 mg/kg, the highest dose tested.

Additional nonclinical information can be obtained from the Investigator Brochure.

1.4 Clinical Experience with MEDI-563

MEDI-563 is being evaluated in 4 clinical studies, including the current study. One study has completed enrollment and data analysis is ongoing (MI-CP158) and the remaining 3 studies are ongoing (MI-CP166, MI-CP186, and MI-CP197). All clinical studies are being conducted in adult subjects with asthma.

The first clinical study of MEDI-563 in humans was MI-CP158, a Phase 1, open-label, dose-escalation study evaluating the safety and tolerability of single IV doses of MEDI-563 (0.003 to 3 mg/kg) in adult subjects with mild asthma. This study has completed enrollment and data analysis is ongoing. A total of 44 subjects have received a single IV dose of MEDI-563 in this study. MEDI-563 was well tolerated in this study. The majority (>85%) of adverse events (AEs) were mild in severity, and there were no deaths, serious adverse events (SAEs), severe AEs, nor any AEs that resulted in MEDI-563 discontinuation. The most common AE was decreased white blood cell count. This finding is consistent with the mechanism of MEDI-563 (ie, depletion of eosinophils in peripheral blood). Another common AE was mild elevations in blood creatine phosphokinase (CPK). A single IV dose of MEDI-563, as low as 0.03 mg/kg, depleted eosinophils in peripheral blood to below the level of detection for at least 8 weeks. In the high-dose groups (1.0 and 3.0 mg/kg), the eosinopenia in peripheral blood lasted up to 12 to 16 weeks, respectively. Conversely, in the low-dose groups (0.003 and 0.0003 mg/kg) eosinopenia in peripheral blood lasted an average of 2 weeks and 1 to 2 days, respectively, demonstrating that the effects of MEDI-563 are dose-dependent.

MI-CP186 is a Phase 2, randomized, double-blind, placebo-controlled study evaluating the effect of two IV dose regimens of MEDI-563 (0.3 and 1.0 mg/kg) on the asthma exacerbation rate (relapse and de novo) in adult subjects who required an urgent healthcare visit for treatment of an acute asthma exacerbation.

MI-CP197 is a Phase 2a, randomized, double-blind, placebo-controlled, dose-escalation study evaluating the safety, tolerability, PK, and immunogenicity (IM) of multiple SC doses of MEDI-

563 (25, 100, and 200 mg) in adult subjects with asthma. All subjects have been treated with no serious safety issues reported.

In the current study (MI-CP166), a total of 13 subjects (Cohort 1) received a single IV dose of MEDI-563 (1.0 mg/kg) or placebo and completed the study according to the protocol. Data remain blinded as per protocol. No SAEs have occurred in any of the subjects in Cohort 1.

Additional clinical information can be obtained from the Investigator Brochure.

1.5 Rationale for Study

This is a Phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and effect of single IV or multiple SC administration of MEDI-563 on airway eosinophils in adults with asthma who have ≥ 2.5% eosinophils in sputum. This inclusion criterion was selected because in the presence of asthma it may identify subjects with higher numbers of eosinophils in airway mucosal biopsies (Lemiere et al, 2006). Previous experience with another anti-IL-5 monoclonal antibody has shown that a dose that provokes less than 60% mean reduction of eosinophils in airway mucosa is unlikely to be clinically effective in asthma (Green et al, 2002).

Initially, 12 subjects will be randomized in a 2:1 ratio to receive a single IV dose of MEDI-563 (1.0 mg/kg) or placebo (Cohort 1). Airway biopsies will be done on Study Day 28. Biopsy results were to be evaluated to determine if the study will continue as a single-dose reduction study or a multiple-dose escalation study. The criterion for this decision was as follows:

- If the Study Day 28 airway biopsy results from Cohort 1 MEDI-563 subjects show the mean number of eosinophils in airway mucosa is reduced from baseline by 80% or more, subsequent cohorts of 12 subjects each (randomized in a 2:1 ratio) will receive a single lower dose of MEDI-563 (0.3, 0.03, 0.003 mg/kg) or placebo until either the dose that provokes less than a 60% mean reduction of eosinophils in airway mucosa is reached or the 0.003 mg/kg dose cohort is enrolled.

- If the Study Day 28 airway biopsy results from Cohort 1 MEDI-563 subjects show the mean number of eosinophils in airway mucosa is reduced from baseline by less than 80%, subsequent cohorts of 12 subjects each (randomized in a 2:1 ratio to receive MEDI-563 or placebo) will receive 4 treatments (every 3 weeks) of MEDI-563 (0.3, 1.0, or 3.0 mg/kg) or placebo until either the dose that provokes a 80% or more mean reduction of eosinophils in airway mucosa or the 3.0 mg/kg dose cohort is enrolled.

The decision tree above was removed to include the evaluation of multiple-dose SC administration (100 mg and 200 mg) instead of single or multiple-dose IV administration of MEDI-563 due to the development of the SC formulation of MEDI-563 and the intent to proceed with multiple-dose SC administration in the future.

A total of 13 subjects received a single IV dose of MEDI-563 (1.0 mg/kg) or placebo (Cohort 1) in this study under previous versions of the study protocol. Cohort 1 completed the study, and the data remain blinded per protocol.

[redacted]

A second group of 12 subjects (Cohort 2) will be randomized in a 1:1:1 ratio to receive 1 of 2 doses of MEDI-563 (100 mg or 200 mg) or placebo as an SC injection once every 4 weeks for 8 weeks (Study Day 0, Study Day 28, and Study Day 56). This cohort may be expanded by up to 3 additional subjects (for a maximum of 15 subjects) if eligible subjects are already in screening at the time 12 subjects have been randomized into the dose cohort.

All subjects will be followed for at least 12 weeks after the last dose of study drug (anticipated to be greater than 5 half-lives of the study drug). If, at the End of Study/Study Termination visit (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2), a subject's eosinophil count in peripheral blood is not at least 100 eosinophils/mm^3 OR the peripheral blood eosinophil count has not returned to at least 70% of the baseline value, the subject will return for follow-up every other month until the eosinophil count meets one of the criteria above.

2 STUDY OBJECTIVES AND OVERVIEW

2.1 Primary Objective(s)

The primary objectives of this study are to:

1. Evaluate the safety and tolerability of MEDI-563 in adults with asthma; and
2. Evaluate the effects of MEDI-563 on eosinophil counts in airway mucosal biopsies 28 days after completion of dosing in adults with asthma.

2.2 Secondary Objective(s)

The secondary objectives of this study are to:

1. Evaluate the PK of MEDI-563 in adults with asthma; and
2. Evaluate the IM of MEDI-563 in adults with asthma.

2.3 Exploratory Objectives

The exploratory objectives of this study are to:

1. Evaluate the effects of MEDI-563 on disease activity;
2. Evaluate the effects of MEDI-563 on inflammatory cells and proteins in mucosal biopsies, including eosinophils in mucosal biopsies;
3. Evaluate the effects of MEDI-563 on inflammatory cells and proteins in induced sputum;
4. Evaluate the effects of MEDI-563 on eosinophils and eosinophil precursors in bone marrow in adults with asthma;
5. Evaluate the effects of MEDI-563 on peripheral blood levels of eosinophil and basophil derived proteins and cytokines in adults with asthma;
6. Evaluate the effects of MEDI-563 on peripheral blood eosinophil and basophil counts;
7. Evaluate downstream effects of MEDI-563 on mRNA levels in whole blood, using microarray analyses; and

[redacted]

8. Explore single-nucleotide-polymorphisms and microsatellite or short tandem repeat analyses for genes associated with asthma in whole blood DNA, if such analyses are warranted based on other exploratory analyses in adults with asthma.

2.4 Overview

2.4.1 Study Design

This is a Phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and effects of single IV and multiple SC administration of MEDI-563 on airway eosinophils in adults with asthma who have ≥ 2.5% eosinophils in sputum. A total of up to 24 subjects are expected to be enrolled at approximately 10 investigative sites in the USA and Canada.

The first 12 subjects will be randomized in a 2:1 ratio to receive a single IV dose of MEDI-563 (1.0 mg/kg) or placebo (Cohort 1), with 8 subjects receiving MEDI-563 and 4 subjects receiving placebo. This cohort may be expanded by up to 3 additional subjects (for a maximum of 15 subjects) if eligible subjects are already in screening at the time 12 subjects have been randomized into the dose cohort. On Study Day 28, these subjects will undergo an airway biopsy. Decisions regarding whether to proceed with single-dose cohorts or multiple-dose cohorts were to be based on these biopsy results as follows:

- If the airway biopsy results from subjects treated with MEDI-563 indicate a mean reduction in eosinophil count of ≥ 80% from baseline (Study Day 0), subsequent cohorts will receive reduced single IV doses of MEDI-563 or placebo.

- If the airway biopsy results from subjects treated with MEDI-563 indicate a mean reduction in eosinophil count of < 80% from baseline (Study Day 0), subsequent cohorts will receive multiple IV doses of MEDI-563 or placebo.

The decision tree above was removed to include the evaluation of multiple-dose SC administration (100 mg and 200 mg) instead of single or multiple-dose IV administration of MEDI-563 due to the development of the SC formulation of MEDI-563 and the intent to proceed with multiple-dose SC administration in the future.

A total of 13 subjects received a single IV dose of MEDI-563 (1.0 mg/kg) or placebo (Cohort 1) in this study under previous versions of the study protocol. Cohort 1 completed the study, and the data remain blinded per protocol.

A second group of 12 subjects (Cohort 2) will be randomized in a 1:1:1 ratio to receive 1 of 2 doses of MEDI-563 (100 mg or 200 mg) or placebo as an SC injection once every 4 weeks for 8 weeks (Study Day 0, Study Day 28, and Study Day 56). This cohort may be expanded by up to 3 additional subjects (for a maximum of 15 subjects) if eligible subjects are already in screening at the time 12 subjects have been randomized into the dose cohort.

Subjects will be screened for up to 14 days. Study drug administration will occur on Study Day 0 for Cohort 1 and on Study Days 0, 28, and 56 for Cohort 2. All subjects will be followed for at

least 12 weeks after receiving the study drug. Subjects in Cohorts 1 and 2 will have bronchoscopies with biopsies consisting of 4-6 subsegmental and segmental biopsies performed at 2 time points during the study (screening and Study Day 28 for Cohort 1 or screening and Study Day 84 for Cohort 2). For Cohort 1 only, an additional optional bronchoscopy and biopsies may be performed on Study Day 84.

The study schema is described in Figure 1.

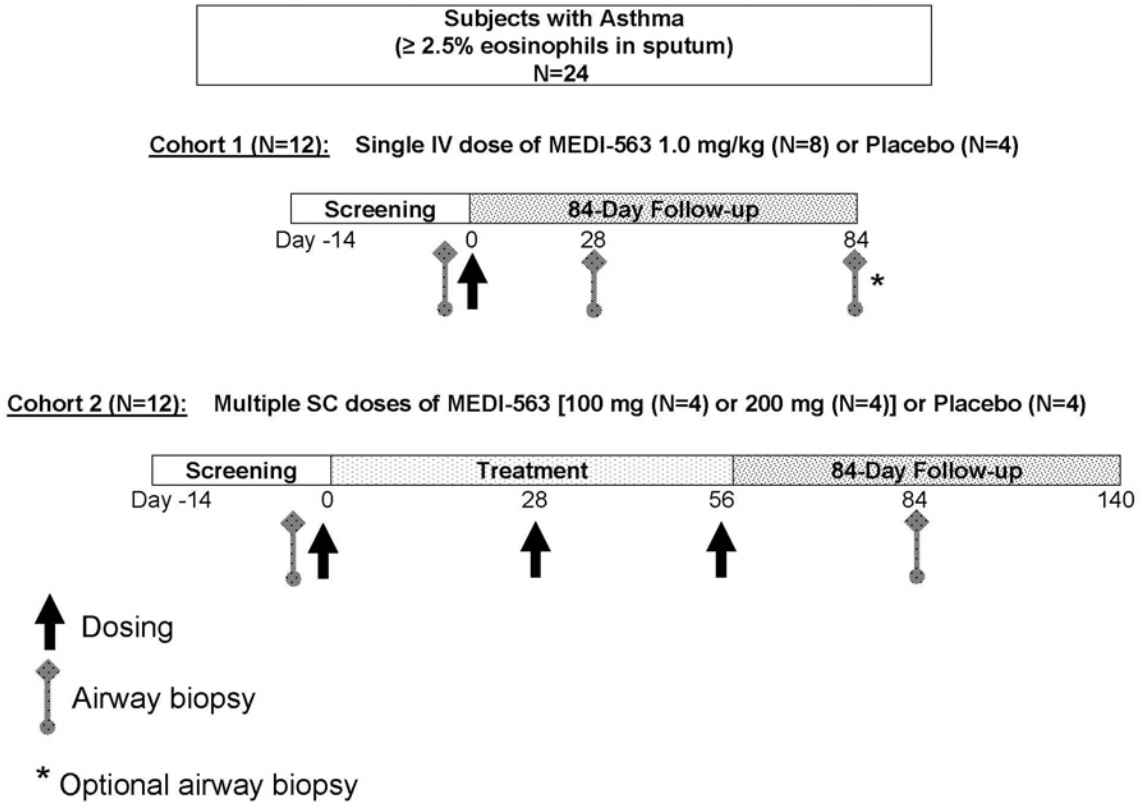

Figure 1 Study Schema.

3 STUDY PROCEDURES

3.1 Subject Selection

The subjects in this study will be adults with asthma who have ≥ 2.5% eosinophils in sputum.

The subject will be counseled by the site investigator (physician) or qualified designee who will discuss the study with him/her, address the questions and concerns of the subject, and secure written informed consent for participation in the study. Written informed consent will be obtained prior to conducting study procedures or administration of study drug.

3.1.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1. Male or female adults, 18 through 65 years of age at time of randomization;
2. Written informed consent obtained from the subject prior to beginning study procedures or receipt of any study medication;
3. Previously documented diagnosis of asthma of ≥ 1 year duration, based on episodic symptoms of airflow obstruction; post-bronchodilator reversibility of airflow obstruction ≥ 12% (in USA only - if subject does not achieve this during screening, proof of ≥12% reversibility within 1 year of randomization is acceptable) or proof of a positive response to a methacholine challenge during screening with prior approval from MedImmune (in USA only - within 1 year of randomization is acceptable) as represented by a provoking concentration of methacholine to cause a 20% fall in FEV_1 (PC_{20}) < 8 mg/ml [American Thoracic Society (ATS), 2000)]; and exclusion of alternative pulmonary diagnoses (eg, cystic fibrosis, COPD);
4. Asthma symptoms are adequately controlled on a therapeutic regimen that has not changed in the last 4 weeks prior to Study Day 0, and the subject is willing to maintain the same therapeutic regimen and doses from the time of screening to the time of the first follow-up bronchoscopy with airway mucosal biopsies (Study Day 28 for Cohort 1; Study Day 84 for Cohort 2);
5. Pre-bronchodilator FEV_1/forced vital capacity (FVC) ratio that is below the age-adjusted normal limit as defined by the 2007 National Heart Lung and Blood Institute Asthma guidelines (Appendix D) and post-bronchodilator $FEV_1 \geq 65\%$ at screening;
6. Must have ≥ 2.5% eosinophils in sputum;
7. Have had no hospitalizations due to asthma in the last year prior to screening;
8. Women of childbearing potential, unless surgically sterile or at least 1 year post-menopausal, must use 2 effective methods of avoiding pregnancy (including oral, transdermal, or implanted contraceptives, intrauterine device, female condom with spermicide, diaphragm with spermicide, cervical cap, abstinence, use of a condom with spermicide by the sexual partner, or sterile sexual partner) for 14 days prior to the first dose of study drug on Study Day 0, and must agree to continue using such precautions through End of Study/Study Termination (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2). Cessation of birth control after this point should be discussed with a responsible physician. Men, unless surgically sterile, with their partners must likewise use 2 effective methods of birth control and must agree to continue using such contraceptive precautions through End of Study/Study Termination (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2);
9. Able to complete the follow-up period as required by the protocol;
10. Willing to forego other forms of experimental treatment and study procedures during the study and during an 84-day period after the last dose of study drug; and
11. Able to provide spirometric readings that meet ATS standards (ATS, 1995)

3.1.2 Exclusion Criteria

Subjects must have *none* of the following:

1. Participation in any previous MEDI-563 clinical study;

[redacted]

2. Known history of allergy or adverse reactions to any component of the study drug formulation;
3. Lung disease other than asthma (eg, COPD, cystic fibrosis, eosinophilic pneumonia);
4. Current use of any systemic or inhaled immunosuppressive drugs [oral (up to a maximum dose of 10 mg/day or 20 mg every other day) and inhaled corticosteroids are allowed if dose has been stable for at least 4 weeks prior to study drug administration on Study Day 0].
5. Current use of any β-blocker (eg, propranolol);
6. Acute illnesses or evidence of clinically significant active infection, such as fever ≥ 38.0ºC (100.5ºF) at screening and through the time of the study drug administration on Study Day 0;
7. Receipt of any investigational drug therapy, intravenous immunoglobulin (IVIG), or monoclonal therapy (eg, Xolair®) within 30 days or within 5-half lives prior to study drug administration on Study Day 0 through End of Study/Study Termination (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2);
8. Pregnancy (women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to study drug administration on Study Day 0);
9. Breastfeeding or lactating;
10. History of alcohol or drug abuse < 1 year prior to Study Day 0;
11. History of cancer, apart from basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy > 1 year prior to Study Day 0;
12. History of a previous episode of active TB or a positive TB skin test without completion of an appropriate course of treatment;
13. A history of coagulation disorders that would contraindicate mucosal biopsies;
14. History of immunodeficiency or infection with HIV-1, HIV-2, or hepatitis A, B, or C virus;
15. History of use of tobacco products within 2 years of baseline (Study Day 0) or history of smoking ≥ 10 pack-years;
16. Elective surgery planned from the time of screening through first follow-up bronchoscopy with airway mucosal biopsies (Study Day 28 or Study Day 84, as applicable);
17. Evidence of any systemic disease or respiratory disease (other than asthma), history of any disease, or any finding upon physical examination, screening laboratory test, chest X-ray (CXR), or ECG that, in the opinion of the investigator or medical monitor, may compromise the safety of the subject in the study or confound the analysis of the study results;
18. Any employee of the research site who is involved with the conduct of the study;
19. History of lidocaine allergy

3.2 Randomization

3.2.1 Subject Randomization Procedures and Treatment Allocation

Subjects will be screened by investigators or qualified designee to assess eligibility for randomization into the study. A screening identification number will be assigned to each subject after he or she signs the informed consent. A master log will be maintained of all screened and consented subjects. Following review of inclusion and exclusion criteria, treatment assignments for Cohort 1 will be determined using a block randomization procedure with a 2:1 ratio through an interactive voice response system (IVRS). Treatment assignments for Cohort 2 will be determined using a block randomization procedure with a 1:1:1 ratio through an IVRS.

[redacted]

The following subjects may be replaced:

Cohort 1

- Subjects who do not receive one dose of investigational product (MEDI-563 or placebo), or
- Subjects who do not have airway mucosal biopsy results at screening and Study Day 28, or
- Subjects who receive a burst of corticosteroids (oral, injectable, IV) within 28 days prior to the second airway biopsy (Study Day 28)

Cohort 2

- Subjects who do not receive 3 doses of investigational product (MEDI-563 or placebo), or
- Subjects who do not have airway mucosal biopsy results at screening and Study Day 84, or
- Subjects who receive a burst of corticosteroids (oral, injectable, IV), or contract an upper or lower respiratory infection requiring antibiotics or antivirals within 28 days prior to the second airway biopsy (Study Day 84)

The replacement subject will receive the same treatment assignment as the corresponding subject being replaced.

The procedure for randomization is as follows:

1. The subject arrives at the clinic or hospital for the Study Day 0 visit;
2. The investigator or qualified designee confirms that the subject meets all eligibility criteria and has signed an informed consent form;
3. The investigator or qualified designee calls the IVRS and provides the subject's initials, screening number, date of birth, sex, and weight;
4. The IVRS randomizes the subject and assigns a participant identification number (PID) and study drug kit (2 kits will be assigned for Cohort 2) to be used for that subject; and
5. A confirmatory fax/e-mail with this information is sent to the investigator or qualified designee.

When a subject is assigned a PID by the IVRS the subject is considered randomized into the study.

For the Study Day 0 dose, the study drug (MEDI-563 or placebo) must be administered as soon as possible after randomization and after baseline procedures are completed on Study Day 0. If there is a delay in the administration of study drug such that it will not be administered on Day 0 or the day after randomization, MedImmune must be notified immediately.

For Cohort 2, subsequent doses must be administered as soon as possible once the kits have been assigned through IVRS. If there is a delay in the administration of study drug such that it will not

[redacted]

be administered on the dosing day (Day 28 or Day 56), MedImmune must be notified immediately.

3.2.2 Blinding

This is a double-blind study. All protocol-associated MedImmune personnel or designees, including the medical monitor, project manager, the statistician, and the site monitors, will be blinded to treatment assignments. In addition, the subject and the clinical site staff including the investigators, study nurses, coordinators, and the Clinical Trial Material Manager (CTMM) will also be blinded. Drug supply management personnel and a limited number of MedImmune personnel who will analyze airway biopsy results, and PK and PD data, will be unblinded during the conduct of the study. Unblinded MedImmune personnel will not be associated with the clinical conduct of the study and will not reveal the treatment assignment of individual subjects to any clinical personnel involved in the study.

Eosinophil and basophil counts in peripheral blood can be a source of unblinding due to the known effects of MEDI-563. Thus, once subjects are treated, eosinophil and basophil counts (including eosinophilic cationic protein (ECP), eosinophilic derived neurotoxin (EDN), and eosinophil- and basophil-derived proteins and cytokines) will not be communicated to the site personnel who evaluate the subjects clinically, except if the information is required for management of AEs or for long-term follow-up of eosinophil counts after the End of Study/Termination visit (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2).

Study drug will be supplied to the pharmacy in vials with identical appearances in coded kits. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each vial within the carton). The clinical site staff will order study drug from the pharmacy using the site's normal ordering procedures. The CTMM will prepare the study drug from one or more of the appropriate vials (determined by the subject's weight for Cohort 1 and randomization assignment for Cohorts 1 and 2). Detailed instructions are in the Clinical Trial Material Manual supplied by MedImmune.

If an investigator feels he/she needs to be unblinded to an individual subject's treatment in order to treat an AE, the investigator should follow the instructions for unblinding contained in the IVRS manual.

In the event the treatment allocation for a subject becomes known to the investigator, the investigator or designated staff must notify MedImmune immediately.

3.3 Study Drug

3.3.1 Study Drug Supplies and Accountability

MEDI-563 is manufactured by AppTec, Inc. The placebo to match MEDI-563 is manufactured by MedImmune. MedImmune will provide the investigators with adequate quantities of MEDI-563 and placebo. MEDI-563 and placebo will be supplied [redacted]. All study drug and placebo will be stored at +2°C to +8°C (36°F to 46°F) and must not be frozen.

[redacted]

The [redacted] of MEDI-563 is as follows:

MEDI-563 MEDI-563 is supplied in [redacted]

Placebo: Placebo is supplied in [redacted]

The [redacted] of MEDI-563 is as follows:

MEDI-563: MEDI-563 is supplied [redacted]

Placebo: Placebo is supplied [redacted]

Specific details regarding study drug supplies, dose preparation, and accountability will be provided in the Clinical Trial Material Manual supplied to the sites.

The CTMM is required to maintain accurate drug accountability records. Upon completion of the study, all study drug accountability records will be returned to the sponsor. All unused study drug will be returned to the distribution center designated by the sponsor.

3.3.2 Treatment Regimen(s)

3.3.2.1 Cohort 1

Subjects in Cohort 1 will receive either MEDI-563 or placebo as an IV infusion (see Table 1). The first 12 subjects will receive MEDI-563 (1.0 mg/kg) or placebo as a single IV infusion on Study Day 0, with 8 subjects receiving MEDI-563 and 4 subjects receiving placebo. All infusions must be administered with a 0.22 μm protein-sparing/low in-line filter, which will be supplied by the sponsor. All doses must be administered over at least 30 minutes.

Table 1 Summary of Study Drug Administration in Cohort 1

Cohort	N	Treatment
1	12	1.0 mg/kg IV: MEDI-563 (N=8) / Placebo (N=4) on Study Day 0

[redacted]

3.3.2.2 Cohort 2

Subjects in Cohort 2 will receive 1 of 2 doses of MEDI-563 (100 mg or 200 mg) or placebo as an SC injection once every 4 weeks on Study Days 0, 28, and 56 (Table 2). Four subjects will receive each MEDI-563 dose and 4 subjects will receive placebo. The study drug will be administered by injection into the SC tissue of the triceps muscle of the arm. All subjects will receive a total of 4 SC injections of MEDI-563 and/or placebo on each dosing day.

Table 2 Summary of Study Drug Administration in Cohort 2

Cohort	N	Treatment
2	4	2 × 50 mg SC MEDI-563 and 2 × SC placebo on Study Days 0, 28, and 56
	4	4 × 50 mg SC MEDI-563 on Study Days 0, 28, and 56
	4	4 × Placebo SC on Study Days 0, 28, and 56

3.3.3 Study Drug Ordering and Preparation

The dose of study drug (MEDI-563 or placebo) for IV and SC administration must be prepared using aseptic technique by the CTMM.

For IV administration, the study drug (MEDI-563 or placebo) will be diluted in 0.9% normal saline and the volume will be standardized to 100 mL for all doses except the 0.003 mg/kg dose, which will be diluted to 10 mL. Detailed instructions regarding study drug preparation can be found in the Clinical Trial Material Manual provided to the CTMM.

The volume of study drug to be diluted is calculated on the basis of the subject's weight (in kg) measured on Study Day 0 using the following formula:

$$\text{Dose (mL)} = \frac{\text{Weight (kg)} \times \text{Dose (mg/kg)}}{5 \text{ mg/mL}}$$

For example: For an 80 kg subject dosed at 1.0 mg/kg MEDI-563, the volume of MEDI-563 required for dilution would be 16.0 mL.

For SC administration, the volume of study drug for each SC injection will be 1.0 mL.

The study drug must be administered within 6 hours after preparation. If the dose is not administered within 6 hours, a new dose must be prepared using a new vial or vials as the study drug product contains no bacteriostatic agents.

[redacted]

3.3.4 Administration of Study Drug

3.3.4.1 Intravenous Administration

In Cohort 1, the study drug should be dispensed by the pharmacist or qualified designee and administered as an IV infusion. Do not administer by IV bolus injection. Table 3 provides dilution and infusion time details per dose for single-dose administration.

All infusions must be administered with a 0.22 µm protein-sparing/low in-line filter, which will be supplied by the sponsor. All doses must be administered over at least 30 minutes.

Some study drug may remain in the IV tubing after the infusion has completed; 30 mL of normal saline will be added to the infusion bag after the study drug has been administered. The infusion rate should not be changed. This will add an additional 9 minutes to the total infusion time.

Table 3 Intravenous Administration in Cohort 1

Cohort	Dose (mg/kg)	Infusion Volume (mL)	Infusion Duration (min)	Infusion Rate (mL/hr)
1	1.0	100	30	200

On Study Day 0, vital signs will be taken prior to drug administration (blood pressure, temperature, pulse rate, and respiratory rate), every 15 minutes during drug administration, and immediately after drug administration. Thereafter, blood pressure and pulse will be checked every 15 minutes for 60 minutes or until stable, whichever is longer, then every hour until the subject is discharged from the study site. Subjects will be observed at the study site for a minimum of 6 hours, during which time adverse reactions to the study drug will be monitored. Vital signs (blood pressure, temperature, pulse rate, respiratory rate) will be checked just prior to discharge; see Section 4.9 for additional information.

3.3.4.2 Subcutaneous Administration

In Cohort 2, the study drug will be administered by SC injection. The investigator or qualified designee will inject the study drug. The SC injections will be administered into the SC tissue of the triceps muscle of the arm. Four injections are required; one injection in each arm should be administered in the region of the upper triceps muscle and one injection in each arm in the region near the lower triceps muscle.

The study drug will be administered via a 26-gauge 3/8-inch needle. The person administering the dose will wipe the skin surface with alcohol and allow to air dry. The skin over the triceps muscle (excluding the muscle) 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 tissues overlaying the triceps muscle. The study drug 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.

[redacted]

Vital signs (blood pressure, temperature, pulse rate, and respiratory rate) will be obtained prior to study drug administration, immediately after study drug administration (+ 5 minutes), and every 30 minutes (± 5 minutes) for 2 hours after study drug administration or until stable, whichever is later. In addition, subjects will be monitored for a minimum of 2 hours for immediate drug reactions after study drug administration.

If a subject has a mild or moderate acute illness (eg, bronchitis) at the time of the second or subsequent scheduled injection of study drug, the injection may be delayed for up to 7 days upon consultation with MedImmune. If the illness does not resolve, the sponsor will be consulted. If any study drug injections are missed, subsequent injections of study drug will be administered as scheduled by the protocol. Subjects with minor illnesses such as diarrhea or a mild upper respiratory tract infection may receive study drug after discussion with the MedImmune medical monitor.

3.3.5 Restricted Medications

All concomitant medications used by the subject from the date the subject signs the informed consent through End of Study/Study Termination (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2) will be recorded on the case report form (CRF). Subjects may not receive the following from screening through End of Study/Study Termination (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2):

1. Immunosuppressive medication (nasal, inhaled*, oral*, and topical corticosteroids are permitted); or
2. β-blocker (eg, propranolol)

* If the subject is receiving ICS or oral corticosteroids (up to a maximum dose of 10 mg/day or 20 mg every other day) the dose should be stable for at least 4 weeks prior to study drug administration on Study Day 0 and remain stable until after the first follow-up bronchoscopy (Study Day 28 for Cohort 1; Study Day 84 for Cohort 2).

Receipt of any of the following will be restricted as follows:

1. Any investigational, non-biologic from 30 days prior to study drug administration on Study Day 0 through End of Study/Study Termination (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2);
2. IVIG or any MAb investigational or marketed product (such as Xolair®) within 5-half lives prior to study drug administration on Study Day 0 through End of Study/Study Termination (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2)

3. Administration of influenza vaccines within 14 days prior to Study Day 0 or Study Day 84 bronchoscopies.

4. Administration of a burst of corticosteroids (oral, injectable, IV), antibiotics and antivirals for an upper or lower respiratory infection will be permitted per the investigator's clinical judgment provided they are completed > 28 days prior to the Study Day 84 bronchoscopy (Cohort 2 only).

[redacted]

The sponsor must be notified if any subject receives prohibited concomitant medications. Subjects may receive medications to treat AEs as deemed necessary by the investigator or qualified designee, or the subject's physician.

3.4 Schedule of Subject Evaluations

All subjects who are assigned a PID and receive any study drug will be followed according to the protocol regardless of the number of doses of study drug received, unless consent for follow-up is withdrawn. The sponsor must be notified of all 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.

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

A schedule of screening and on-study visit procedures is presented in Table 4 for Cohort 1 and Table 5 for Cohort 2, followed by a detailed description of each visit.

Table 4 Study Schedule for Cohort 1

Study Day	Screening (-14 D to -1 D)	0	1	7	21	28	56	77	84 (End of Study / Study Termination)	Long-term Follow-up [f]
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
ELIGIBILITY										
Written Informed Consent	X									
Verify Eligibility Criteria	X	X				X				
Medical History and Asthma History	X	X								
Physical Examination	X	X				X			X	
Body Height	X									
Body Weight	X	X								
Chest X-ray (CXR)	X									
Mantoux (PPD) Test	X									
HIV-1, HIV-2; Hepatitis A, B, C	X									
Serum βHCG [a]	X									
Urine βHCG [a]		X							X	
Record Concomitant Medications	X	X	X	X	X	X	X	X	X	
STUDY DRUG ADMINISTRATION		**X**								
SAFETY										
Vital Signs	X	X	X	X	X	X	X	X	X	
Assess AEs/SAEs	X	X	X	X	X	X	X	X	X	X [g]
CBC with Differentials and Platelets	X	X	X	X		X	X		X	X
Serum Chemistry	X	X	X	X		X	X		X	
PT/PTT	X									
Serum CRP, ECP, EDN, IL-5,and IL-6		X	X	X		X	X		X	
Urinalysis	X	X	X	X		X	X		X	
12-lead ECG	X					X			X	
DISEASE ACTIVITY										
Skin Prick Test	X									
Assess eNO [b]		X				X	X		X	
Spirometry at Site	X	X	X	X	X	X	X	X	X	
Collect Subject Home Peak Flow Monitoring, Use Of Rescue β2 Agonists		X	X	X	X	X	X	X	X	
Asthma Control Questionnaire (ACQ)		X		X		X	X	X	X	
AQLQ(S)		X				X	X		X	

[redacted]

Study Day	Screening (-14 D to -1 D)	0	1	7	21	28	56	77	84 (End of Study / Study Termination)	Long-term Follow-up [f]
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
CORRELATIVE STUDIES										
Bronchoscopy with Airway Mucosal Biopsies	X [c]					X			X [d]	
Sputum Induction and Collection	X				X		X	X		
Bone Marrow Aspiration [e]	X					X				
Serum for Eosinophil- and Basophil-derived Proteins, Cytokines		X	X	X		X			X	
Serum and Whole Blood for RNA for Storage		X		X		X	X		X	
DNA Sample		X								
PK/IM										
MEDI-563 Plasma Concentration		X	X	X		X	X		X	
Anti-MEDI-563 Antibodies		X				X			X	

Table 4 Footnotes:

a For women of childbearing potential, unless surgically sterile or 1 year postmenopausal. Serum ßHCG at screening and urine ßHCG on Study Day 0 must be negative prior to administration of the study drug.
b Exhaled nitric oxide (eNO) must occur before spirometry.
c Bronchoscopy with airway mucosal biopsies needs to be completed 7 (± 1 day) days after the screening sputum induction, and within 2 days prior to Study Day 0 (study drug administration).
d Study Day 84 bronchoscopy is optional.
e Bone marrow aspiration is optional.
f If at the End of Study/Study Termination Visit (Study Day 84) eosinophil levels in peripheral blood are not returned to at least 100 eosinophils/mm^3 OR the peripheral blood eosinophil count has not returned to at least 70% of the baseline value, subjects will return to the study site every other month for additional evaluations.
g SAEs only.

[redacted]

Table 5 Study Schedule for Cohort 2

Study Day	Screening (-14 D to -1 D)	0	1	7	21	28	56	77	84	119	140 (End of Study / Study Termination)	Long-term Follow-up [e]
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
ELIGIBILITY												
Written Informed Consent	X											
Verify Eligibility Criteria	X	X										
Medical History and Asthma History	X	X										
Physical Examination	X	X				X	X		X		X	
Body Height	X											
Body Weight	X											
Chest X-ray (CXR)	X											
Mantoux (PPD) Test	X											
HIV-1, HIV-2; Hepatitis A, B, C	X											
Serum ßHCG [a]	X											
Urine βHCG [a]		X				X	X				X	
Record Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Randomization and Assignment of PID		X										
STUDY DRUG ADMINISTRATION		**X**				**X**	**X**					
SAFETY												
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	
Assess AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X [g]
Assess Injection Sites		X	X	X	X	X	X	X				
CBC with Differentials and Platelets	X	X	X	X	X	X	X		X	X	X	X
Serum Chemistry	X	X	X	X	X	X	X		X	X	X	
PT/PTT	X											
Serum CRP, ECP, EDN, IL-5, and IL-6		X	X	X	X	X	X		X	X	X	
Serum Tryptase		X				X			X			
Urinalysis	X	X	X	X	X	X	X		X	X	X	
12-lead ECG	X								X		X	
DISEASE ACTIVITY												
Skin Prick Test	X											
Assess eNO [b]		X				X			X		X	
Spirometry at Site	X	X	X	X	X	X	X	X	X	X	X	
Collect Subject Home Peak Flow Monitoring, Use of Rescue β2 Agonists		X	X	X	X	X	X	X	X	X	X	

[redacted]

Study Day	Screening (-14 D to -1 D)	0	1	7	21	28	56	77	84	119	140 (End of Study / Study Termination)	Long-term Follow-up [e]
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Asthma Control Questionnaire (ACQ)		X		X		X	X		X	X	X	
AQLQ(S)		X				X	X		X		X	
CORRELATIVE STUDIES												
Bronchoscopy with Airway Mucosal Biopsies	X [c]								X			
Sputum Induction and Collection	X					X		X		X	X	
Bone Marrow Aspiration [d]	X								X			
Serum for Eosinophil- and Basophil-derived Proteins, Cytokines		X	X	X		X	X		X		X	
Whole blood for WBC counts (flow cytometry) [f]		X	X	X		X	X		X		X	
Serum and Whole Blood for RNA for Storage		X		X		X	X		X		X	
DNA Sample		X										
PK/IM												
MEDI-563 Plasma Concentration		X	X	X	X	X	X		X	X	X	
Anti-MEDI-563 Antibodies		X				X			X		X	

Table 5 Footnotes:

a For women of childbearing potential, unless surgically sterile or 1 year postmenopausal. Serum ßHCG at screening and urine ßHCG on Study Days 0, 28, and 56 must be negative prior to administration of the study drug.
b Exhaled nitric oxide (eNO) must occur before spirometry.
c Bronchoscopy with airway mucosal biopsies needs to be completed at least 7 days after the screening sputum induction, and within 2 days prior to Study Day 0 (study drug administration).
d Bone marrow aspiration is optional.
e If at the End of Study/Study Termination Visit (Study Day 140) eosinophil levels in peripheral blood are not at least 100 eosinophils/mm^3 OR the peripheral blood eosinophil count has not returned to at least 70% of the baseline value, subjects will return to the study site every other month for additional evaluations.
f Two separate samples will be drawn.
g SAEs only.

[redacted]

3.4.1 Study Procedures for Cohort 1

All subjects in Cohort 1 will receive study drug on Study Day 0 only.

Screening

All screening laboratory assessments must be performed within 14 days before Study Day 0. The screening evaluations may be carried out over more than 1 visit. Written informed consent must be obtained prior to performing any study-related procedure, including screening evaluations. Screening laboratory test results must be reviewed by the investigator or qualified designee, prior to Study Day 0. Clinically significant abnormal results on screening laboratory tests may be repeated once at the discretion of the site investigator(s) or qualified designee. If a CXR was performed within 6 months prior to screening or if a positive skin prick test was obtained, they need not be repeated if results are obtainable and the subject consents to allow their use.

The following evaluations must be completed within 14 days prior to Study Day 0:

1. Written informed consent
2. Verify eligibility criteria
3. Screening medical history, including history of tobacco use and asthma history
4. Screening physical examination, including body height and weight
5. Assess AEs, and SAEs
6. Review and record concomitant medications
7. Vital signs, including temperature, blood pressure, pulse rate, and respiratory rate
8. 12-lead ECG
9. Urinalysis
10. CXR (may be omitted if subject has documentation of previous x-ray in last 6 months)
11. Mantoux (PPD) test
12. Skin prick test (may be omitted if subject has documentation of a previous skin prick test)
13. Spirometry at site
14. Sputum induction and collection to evaluate eosinophil counts
15. Blood collection for screening
    - Screening chemistry panel (see Section 3.5.5 for details)
    - CBC with differential
    - Prothrombin time (PT)/Partial thromboplastin time (PTT)
    - Serum for hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody and HIV-1 and HIV-2 antibody
    - Serum βHCG (for women of childbearing potential and are not surgically sterile or at least 1 year post-menopausal)
16. Provide subjects with the electronic peak flow monitor to record home peak flow results and use of rescue β2 agonists.

Results from all the tests listed above should be obtained and reviewed prior to the bronchoscopy or bone marrow aspiration.

[redacted]

The following tests should only be completed after all other study eligibility criteria are met.

1. Bone marrow aspirates (optional test that requires signing a separate informed consent form)
2. Bronchoscopy with airway mucosal biopsies

The bronchoscopy with airway mucosal biopsies needs to be completed 7 days (± 1 day) after the sputum induction, and within 2 days prior to Study Day 0 (study drug administration).

Study Day 0: Study Drug Administration (Visit 1)

The following procedures will be completed prior to study drug administration:

1. ACQ
2. AQLQ(S)
3. Verify eligibility criteria
4. Update screening medical history and physical examination (any new findings since screening)
5. eNO (prior to spirometry)
6. Spirometry at site
7. Assess AEs or SAEs since last visit
8. Body weight
9. Record concomitant medications
10. Vital signs (temperature, blood pressure, pulse rate, respiratory rate) prior to administration of study drug
11. Baseline blood collection – prior to study drug administration for:
    - Serum chemistry
    - CBC with differential
    - Serum CRP, ECP, EDN, IL-5, and IL-6
    - MEDI-563 plasma concentration
    - Serum and whole blood for RNA for storage
    - Anti-MEDI-563 antibodies
    - Serum for eosinophil- and basophil-derived proteins, cytokines
    - DNA sample (optional test that requires signing a separate informed consent form)
11. Urinalysis
12. Urine βHCG (for women of childbearing potential and are not surgically sterile or at least 1 year post-menopausal) must have negative result prior to study drug administration
13. Collect subject's daily home peak flow results and rescue β2 agonist use
14. Randomization and assignment of PID.

Study Drug Administration

1. Vital signs (including temperature, blood pressure, pulse rate, and respiratory rate) will be taken as follows:
    - Prior to study drug administration
    - Immediately after study drug administration
    - Every hour until discharge from the study site

[redacted]

- Just prior to discharge

2. Only blood pressure and radial pulse rate will be taken as follows:
   - Every 15 minutes during study drug administration
3. Administer Study Drug
4. Blood draw for MEDI-563 plasma concentration **2 hours** after completion of study drug infusion.
5. Blood draw for serum CRP, ECP, and IL-6 analysis **6 hours** after study drug administration.

Study Day 1 (+ 1 day): (Visit 2)

The following procedures will be completed:

1. Record any changes to concomitant medications
2. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
3. Assess AEs and SAEs
4. Blood collection for:
   - Serum chemistry
   - CBC with differential
   - Serum CRP, ECP, EDN, IL-5, and IL-6
   - Serum for eosinophil and basophil derived proteins, cytokines
   - MEDI-563 plasma concentration
5. Urinalysis
6. Spirometry at site
7. Collect subject's daily home peak flow results and rescue β2 agonist use.

Study Day 7 (± 1 day): (Visit 3)

The following procedures will be completed:

1. ACQ
2. Record any changes to concomitant medications
3. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
4. Assess AEs and SAEs
5. Blood collection for:
   - Serum chemistry
   - CBC with differential
   - Serum CRP, ECP, EDN, IL-5,and IL-6
   - Serum for eosinophil and basophil derived proteins, cytokines
   - Serum and whole blood for RNA for storage
   - MEDI-563 plasma concentration
6. Urinalysis
7. Spirometry at site
8. Collect subject's daily home peak flow results and rescue β2 agonist use.

[redacted]

Study Day 21 (± 2): (Visit 4)

The following procedures will be completed:

1. Sputum induction and collection
2. Spirometry at site
3. Record any changes to concomitant medications
4. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
5. Assess AEs and SAEs
6. Collect subject's daily home peak flow results and rescue β2 agonist use

Study Day 28 (±3): (Visit 5)

This visit must be at least 7 days after Study Day 21 as the bronchoscopy must be at least 7 days after the sputum induction. The following procedures will be completed:

1. ACQ
2. AQLQ(S)
3. Verify eligibility criteria
4. Physical examination
5. Record any changes to concomitant medications
6. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
7. Assess AEs and SAEs
8. Blood collection for:
   - Serum chemistry
   - CBC with differential
   - Serum CRP, ECP,EDN, IL-5, and IL-6
   - Serum for eosinophil and basophil derived proteins, cytokines
   - Anti-MEDI-563 antibodies
   - Serum and whole blood for RNA for storage
   - MEDI-563 plasma concentration
9. Urinalysis
10. 12-lead ECG
11. eNO (prior to spirometry)
12. Spirometry at site (before and after the bronchoscopy)
13. Collect subject's daily home peak flow results and rescue β2 agonist use
14. Bronchoscopy with airway mucosal biopsies
15. Bone marrow (optional).

Study Day 56 (± 3): (Visit 6)

The following procedures will be completed:

1. ACQ
2. AQLQ(S)
3. Record any changes to concomitant medications
4. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)

[redacted]

5. Assess AEs and SAEs
6. Blood collection for:
   - Serum chemistry
   - CBC with differential
   - Serum CRP, ECP,EDN, IL-5, and IL-6
   - MEDI-563 plasma concentration
7. Urinalysis
8. eNO (prior to spirometry)
9. Spirometry at site
10. Collect subject's daily home peak flow results and rescue β2 agonist use
11. Sputum induction and collection.

Study Day 77 (±3): (Visit 7)

The following procedures will be completed:

1. ACQ
2. Sputum induction and collection
3. Spirometry at site
4. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate).
5. Assess AEs and SAEs
6. Record any changes to concomitant medications
7. Collect subject's daily home peak flow results and rescue β2 agonist use.

Study Day 84 (±3): End of Study/Study Termination (Visit 8)

This visit must be at least 7 days after Study Day 77 as the bronchoscopy must be at least 7 days after the sputum induction. The procedures listed below will be completed on Study Day 84 or when a subject discontinues participation in the study early. If a particular evaluation was performed within 2 weeks prior to the discontinuation visit, it need not be repeated, with the exception that all subjects will be requested to have airway mucosal biopsies done at least once following dosing. The following procedures will be completed:

1. ACQ
2. AQLQ(S)
3. Physical Examination
4. Record any changes to concomitant medications
5. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
6. Assess AEs and SAEs
7. Blood collection for:
   - Serum chemistry
   - CBC with differential
   - Serum CRP, ECP, EDN, IL-5, and IL-6
   - Anti-MEDI-563 antibodies
   - Serum for eosinophil and basophil derived proteins, cytokines
   - Serum and whole blood for RNA for storage

[redacted]

- MEDI-563 plasma concentration

8. Urinalysis
9. 12-lead ECG
10. Urine ßHCG
11. eNO (prior to spirometry)
12. Spirometry at site (before and after the bronchoscopy)
13. Collect subject's daily home peak flow results and rescue β2 agonist use
14. Bronchoscopy with airway mucosal biopsies (optional).

Long-term Follow-up

If, at the End of Study/Study Termination visit (Study Day 84), eosinophil levels in peripheral blood are not at least 100 eosinophils/mm^3 OR the peripheral blood eosinophil count has not returned to at least 70% of the baseline value, subjects will be asked to return to the study site every other month for the following assessments:

1. Collect blood for:
   - CBC with differential
2. Assess for SAEs

3.4.2 Study Procedures for Cohort 2

Subjects in Cohort 2 will receive study drug on Days 0, 28, and 56.

Screening

All screening laboratory assessments must be performed within 14 days before Study Day 0. The screening evaluations may be carried out over more than 1 visit. Written informed consent must be obtained prior to performing any study-related procedure, including screening evaluations. Screening laboratory test results must be reviewed by the investigator or qualified designee, prior to Study Day 0. Clinically significant abnormal results on screening laboratory tests may be repeated once at the discretion of the site investigator(s) or qualified designee. If a CXR was performed within 6 months prior to screening or if a positive skin prick test was obtained, they need not be repeated if results are obtainable and the subject consents to allow their use.

The following evaluations must be completed within **14 days** prior to Study Day 0:

1. Written informed consent
2. Verify eligibility criteria
3. Screening medical history, including history of tobacco use and comprehensive asthma history
4. Screening physical examination, including body height and weight
5. Assess AEs and SAEs
6. Review and record concomitant medications
7. Vital signs, including temperature, blood pressure, pulse rate, and respiratory rate
8. 12-lead ECG
9. Urinalysis

[redacted]

10. CXR (may be omitted if subject has documentation of previous x-ray in last 6 months)
11. Mantoux (PPD) test
12. Skin prick test (may be omitted if subject has documentation of a previous skin prick test)
13. Spirometry at site
14. Sputum induction and collection to evaluate eosinophil counts
15. Blood collection for screening
    - Screening chemistry panel (see Section 3.5.5 for details)
    - CBC with differential
    - Prothrombin time (PT)/Partial thromboplastin time (PTT)
    - Serum for hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody and HIV-1 and HIV-2 antibody
    - Serum βHCG (for women of childbearing potential and are not surgically sterile or at least 1 year post-menopausal)
16. Provide subjects with electronic home peak flow meter to collect peak flow results at home and use of rescue β2 agonists.

Results from all the tests listed above should be obtained and reviewed prior to the bronchoscopy or bone marrow aspiration. The following tests should only be completed after all other study eligibility criteria are met.

1. Bone marrow aspirates (optional test that requires signing a separate informed consent form)
2. Bronchoscopy with airway mucosal biopsies

The bronchoscopy with airway mucosal biopsies needs to be completed at least 7 days after the sputum induction, and within 2 days of Study Day 0 (study drug administration).

Study Day 0: Study Drug Administration (Visit 1)

The following procedures will be completed prior to study drug administration:

1. ACQ
2. AQLQ(S)
3. Verify eligibility criteria
4. Update screening medical and asthma history and physical examination (any new findings since screening)
5. eNO (prior to spirometry)
6. Spirometry at site
7. Assess AEs or SAEs since last visit
8. Record concomitant medications
9. Vital signs (temperature, blood pressure, pulse rate, respiratory rate) prior to administration of study drug
10. Baseline blood collection – prior to study drug administration for:
    - Serum chemistry
    - CBC with differential
    - Serum CRP, ECP, EDN, IL-5,and IL-6
    - Serum tryptase

- MEDI-563 plasma concentration
- Whole blood for WBC counts (flow cytometry) - 2 separate samples must be collected
- Serum and whole blood for RNA for storage
- Anti-MEDI-563 antibodies
- Serum for eosinophil- and basophil-derived proteins, cytokines
- DNA sample (optional test that requires signing a separate informed consent form)

11. Urinalysis
12. Urine βHCG (for women of childbearing potential and are not surgically sterile or at least 1 year post-menopausal) must have negative result prior to study drug administration
13. Collect subject's daily home peak flow results and rescue β2 agonist use
14. Randomization and assignment of PID.

Study Drug Administration

1. Administer Study Drug
2. Vital signs (including temperature, blood pressure, pulse rate, and respiratory rate) will be taken as follows:
   - Immediately after study drug administration (+ 5 minutes)
   - Every 30 minutes (± 5 minutes) for 2 hours after study drug administration or until stable, whichever is later
3. Assess injection sites
4. Blood draw for MEDI-563 concentration and serum CRP, ECP, and IL-6 analysis **2 hours** after completion of study drug administration.

Study Day 1 (+ 1 day): (Visit 2)

The following procedures will be completed:

1. Record any changes to concomitant medications
2. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
3. Assess AEs and SAEs
4. Assess injection sites
5. Blood collection for:
   - Serum chemistry
   - CBC with differential
   - Serum CRP, ECP, EDN, IL-5, and IL-6
   - Serum for eosinophil and basophil derived proteins, cytokines
   - MEDI-563 plasma concentration
   - Whole blood for WBC counts (flow cytometry) - 2 separate samples must be collected
6. Urinalysis
7. Spirometry at site
8. Collect subject's daily home peak flow results and rescue β2 agonist use.

[redacted]

Study Day 7 (± 1 day): (Visit 3)

The following procedures will be completed:

1. ACQ
1. Record any changes to concomitant medications
2. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
3. Assess AEs and SAEs
4. Assess injection sites
5. Blood collection for:
   - Serum chemistry
   - CBC with differential
   - Serum CRP, ECP, EDN, IL-5, and IL-6
   - Serum for eosinophil and basophil derived proteins, cytokines
   - Whole blood for WBC counts (flow cytometry) - 2 separate samples must be collected
   - Serum and whole blood for RNA for storage
   - MEDI-563 plasma concentration
6. Urinalysis
7. Spirometry at site
8. Collect subject's daily home peak flow results and rescue β2 agonist use.

Study Day 21 (± 2): (Visit 4)

The following procedures will be completed:

1. Record any changes to concomitant medications
2. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) prior to study drug administration
3. Assess AEs and SAEs
4. Assess injection sites
5. Blood collection for:
   - Serum chemistry
   - CBC with differential
   - MEDI-563 plasma concentration
   - Serum CRP, ECP, EDN, IL-5, and IL-6
6. Urinalysis
7. Spirometry at site
8. Collect subject's daily home peak flow results and rescue β2 agonist use.

Study Day 28(± 3): Study Drug Administration (Visit 5)

The following procedures will be completed prior to administration of study drug:

1. ACQ
2. AQLQ(S)
3. Record any changes to concomitant medications

[redacted]

4. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) prior to study drug administration
5. Physical examination
6. Assess AEs and SAEs
7. Assess injection sites
8. Blood collection for:
   - Serum chemistry
   - CBC with differential
   - Serum for eosinophil and basophil derived proteins, cytokines
   - Serum CRP, ECP, EDN, IL-5, and IL-6
   - Serum tryptase
   - Whole blood for WBC counts (flow cytometry) - 2 separate samples must be collected
   - Serum and whole blood for RNA for storage
   - MEDI-563 plasma concentration
   - Anti-MEDI-563 antibodies
9. Urinalysis
10. Urine ßHCG (for women of childbearing potential and are not surgically sterile or at least 1 year post-menopausal) negative result must be obtained prior to study drug administration
11. eNO (prior to spirometry)
12. Spirometry at site
13. Sputum induction and collection
14. Collect subject's daily home peak flow results and rescue β2 agonist use.

Study Drug Administration

1. Administer Study Drug
2. Vital signs (including temperature, blood pressure, pulse rate, and respiratory rate) will be taken as follows:
   - Immediately after study drug administration (+ 5 minutes)
   - Every 30 minutes (± 5 minutes) for 2 hours after study drug administration or until stable, whichever is later
3. Assess injection sites
4. Blood draw for serum CRP, ECP, and IL-6 analysis **2 hours** after completion of study drug administration.

Study Day 56 (± 3): Study Drug Administration (Visit 6)

The following procedures will be completed prior to administration of study drug:

1. ACQ
2. AQLQ(S)
3. Record any changes to concomitant medications
4. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) prior to study drug administration
5. Physical examination
6. Assess AEs and SAEs

[redacted]

7. Assess injection sites
8. Blood collection for:
   - Serum chemistry
   - CBC with differential
   - Serum for eosinophil and basophil derived proteins, cytokines
   - Serum CRP, ECP, EDN, IL-5, and IL-6
   - Whole blood for WBC counts (flow cytometry) - 2 separate samples must be collected
   - Serum and whole blood for RNA for storage
   - MEDI-563 plasma concentration
9. Urinalysis
10. Urine ßHCG (for women of childbearing potential and are not surgically sterile or at least 1 year post-menopausal) negative result must be obtained prior to study drug administration
11. Spirometry at site
12. Collect subject's daily home peak flow results and rescue β2 agonist use

Study Drug Administration

1. Administer Study Drug
2. Vital signs (including temperature, blood pressure, pulse rate, and respiratory rate) will be taken as follows:
   - Immediately after study drug administration (+ 5 minutes)
   - Every 30 minutes (± 5 minutes) for 2 hours after study drug administration or until stable, whichever is later
3. Assess injection sites
4. Blood draw for serum CRP, ECP, and IL-6 analysis **2 hours** after completion of study drug administration.

Study Day 77 (± 7) (Visit 7)

The following procedures will be completed:

1. Spirometry at site
2. Sputum induction and collection
3. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
4. Assess AEs and SAEs
5. Assess injection sites
6. Record any changes to concomitant medications
7. Collect subject's daily home peak flow results and rescue β2 agonist use

Study Day 84 (+7) (Visit 8)

This visit must be at least 7 days after Study Day 77 as the bronchoscopy must be at least 7 days after the sputum induction. The following procedures will be completed:

1. ACQ
2. AQLQ(S)

[redacted]

3. Record any changes to concomitant medications
4. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
5. Assess AEs and SAEs
6. Physical Examination
7. Blood collection for:
   - Serum chemistry
   - CBC with differential
   - Serum CRP, ECP, EDN, IL-5, and IL-6
   - Serum tryptase
   - MEDI-563 plasma concentration
   - Serum for eosinophil and basophil derived proteins, cytokines
   - Whole blood for WBC counts (flow cytometry) - 2 separate samples must be collected
   - Serum and whole blood for RNA for storage
   - Anti-MEDI-563 antibodies
8. Urinalysis
9. 12-lead ECG
10. eNO (prior to spirometry)
11. Spirometry at site
12. Bronchoscopy with airway mucosal biopsies
13. Bone Marrow (optional)
14. Collect subject's daily home peak flow results and rescue β2 agonist use.

Study Day 119 (± 7) (Visit 9)

The following procedures will be completed:

1. ACQ
2. Record any changes to concomitant medications
3. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
4. Assess AEs and SAEs
5. Blood collection for:
   - Serum chemistry
   - CBC with differential
   - Serum CRP, ECP, EDN, IL-5, and IL-6
   - MEDI-563 plasma concentration
6. Urinalysis
7. Spirometry at site
8. Sputum induction and collection
9. Collect subject's daily home peak flow results and rescue β2 agonist use.

[redacted]

Study Day 140 (± 7): End of Study/Study Termination Visit (Visit 10)

The procedures listed below will be completed on Study Day 140 or when a subject discontinues participation in the study early. If this is an early discontinuation visit, a particular evaluation that was performed within 2 weeks prior to this need not be repeated, with the exception that all subjects will be requested to have airway mucosal biopsies done at least once following dosing.

1. ACQ
2. AQLQ(S)
3. Physical Examination
4. Record any changes to concomitant medications
5. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
6. Assess AEs and SAEs
7. Blood collection for:
   - Serum chemistry
   - CBC with differential
   - Serum CRP, ECP, EDN, IL-5, and IL-6
   - MEDI-563 plasma concentration
   - Serum for eosinophil and basophil derived proteins, cytokines
   - Whole blood for WBC counts (flow cytometry) - 2 separate samples must be collected
   - Serum and whole blood for RNA for storage
   - Anti-MEDI-563 antibodies
8. Urinalysis
9. Urine ßHCG (for women of childbearing potential and are not surgically sterile or at least 1 year post-menopausal)
10. 12-lead ECG
11. eNO (prior to spirometry)
12. Spirometry at site
13. Sputum induction and collection
14. Collect subject's daily home peak flow results and rescue β2 agonist use.

Long-term Follow-up

If, at the End of Study/Study Termination visit (Study Day 140), eosinophil levels in peripheral blood are not at least 100 eosinophils/mm^3 OR the peripheral blood eosinophil count has not returned to at least 70% of the baseline value, subjects will be asked to return to the study site every other month for the following assessments:

1. Collect blood for:
   - CBC with differential
2. Assess for SAEs

[redacted]

3.5 Subject Evaluation Methods

3.5.1 Medical History

A complete medical history by body system will be completed during screening. The medical history will also include an asthma history.

For Cohort 2, an asthma history questionnaire will be completed during screening and includes questions related to the subject's asthma history, asthma medications, asthma-related emergency department visits, and asthma-related hospitalizations.

3.5.2 Physical Examinations

Physical examinations will be performed at intervals designated on the study schedule. The examination will include the following assessments:

- Head, eyes, ears, nose, and throat
- Respiratory
- Cardiovascular
- Gastrointestinal
- Musculoskeletal
- Neurological
- Dermatological
- Lymphatic
- Endocrine system
- Body weight
- Body height (screening only)

The weight determined on Study Day 0 will be used for dosing calculations for Cohort 1 only. Medically significant changes from the screening physical examination will be considered AEs and recorded as such on the CRFs.

3.5.3 Chest X-ray

Chest X-rays will be completed during the screening period. The CXR may be substituted with documentation of a previous CXR performed within the previous 6 months that meets inclusion criteria.

3.5.4 Mantoux (PPD) Test for Tuberculin Skin Test

A PPD test must be completed during screening. The PPD test should be one of the first evaluations completed as part of screening, but no less than 48 hours prior to the bronchoscopy, so results will be available prior to the bronchoscopy. Subjects who report a previously positive reaction will not be tested. Study site staff will give the subject an intradermal injection containing 5 tuberculin units in the skin of their forearm, or will follow the package insert for the PPD kit provided. Mantoux tests will be reviewed 48-72 hours after administration. A positive

[redacted]

result will be based on > 15 mm of induration or the presence of blisters. Subjects with a positive reaction will be excluded from the study if appropriate prophylaxis cannot be determined.

3.5.5 Laboratory Evaluations

Routine laboratory tests during screening and during the study will be performed in a licensed central clinical laboratory. A laboratory manual will be provided specifying specific procedures for collection, processing, storage, and shipping of samples. Clinically significant abnormal laboratory results should be repeated as soon as possible (preferably within 24-48 hours). Routine laboratory assessments include the following:

- CBC with differential
- Serum chemistry to include, albumin, amylase, calcium, creatinine, CPK, random glucose, BUN, uric acid, total cholesterol, triglycerides, total protein, bilirubin, ALT, LDH, AST, GGT, sodium, potassium, bicarbonate, and chloride. A fractionated CPK will be completed for any samples that yield an elevated CPK value.
- PT/PTT
- Serum for hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody and HIV-1 antibody
- Serum ßHCG during screening only, for women of childbearing potential, unless surgically sterile or at least 1 year postmenopausal.
- Urinalysis
- Urine pregnancy tests will be preformed using a licensed test prior to study drug administration (Day 0 for Cohort 1 and Days 0, 28, and 56 for Cohort 2) and at the End of Study/Study Termination visit (Day 84 for Cohort 1 or Day 140 for Cohort 2) for women of childbearing potential, unless surgically sterile or at least 1 year postmenopausal.

Additional laboratory tests are listed below. A laboratory manual will be provided specifying specific procedures for collection, processing, storage, and shipping of samples.

- Serum for eosinophil and basophil derived proteins and cytokines
- Serum CRP, ECP, EDN, IL-5, and IL-6.
    - Serum CRP, ECP, and IL-6 will be drawn twice on days study drug is administered (Day 0 for Cohort 1 and Days 0, 28, and 56 for Cohort 2). On days of study drug administration, 1 sample will be drawn just prior to study drug administration and the other sample will be drawn as follows:
    - Cohort 1: 6 hours after study drug administration
    - Cohort 2: 2 hours after study drug administration
- Serum tryptase
- Whole blood for WBCs using flow cytometry (Cohort 2 only). Two samples will be collected. One sample will go to MedImmune and one sample will go to the central clinical laboratory. These samples will be tested for natural killer (NK) cell counts, eosinophil counts, and basophil counts.
- For the purpose of transcript profiling, whole blood in PAXgene RNA tubes will be collected at Study Day 0 (pre-dose) and on Study Days 7, 28, and 84 for Cohort 1, and at Study Day 0

[redacted]

(pre-dose) and on Study Days 7, 28, 84, and 140 for Cohort 2. Affymetrix whole genome array will be used for transcript profiling to examine downstream effect of MEDI-563

- For genotyping, blood in PAXgene DNA tubes will be collected prior to study drug administration on Study Day 0. Tests that may be conducted in these samples include single nucleotide polymorphisms and microsatellite or short tandem repeat analyses for genes associated with asthma.

3.5.6 ECG

A 12-lead ECG will be done during the study according to investigative site procedures. The principal investigator or qualified designee will review and indicate if the ECG is normal or abnormal. Any medically significant changes from the screening ECG will be recorded as an AE.

3.5.7 Concomitant Medications

All concomitant medications will be recorded on the concomitant medication CRF from screening through End of Study/Study Termination. The medication, dose, unit, frequency, route, start date, stop date, and indication will be captured. In addition, if at End of Study/Study Termination, the subject is continuing on a medication, the ongoing box shall be checked instead of a stop date.

3.5.8 Vital Signs

Vital signs, including temperature, blood pressure, pulse rate, and respiratory rate will be recorded at every visit.

For IV administration of study drug, vital signs will be obtained prior to study drug administration, every 15 minutes during study drug administration, immediately after study drug administration, and just prior to discharge from the study site. In addition, blood pressure and radial pulse rate will be obtained every 15 minutes after study drug administration for 60 minutes or until stable, whichever is longer, and then every hour until discharge.

For SC administration of study drug, vital signs will be obtained prior to study drug administration, immediately after study drug administration (+ 5 minutes), and every 30 minutes (± 5 minutes) for 2 hours after study drug administration or until stable, whichever is later.

3.5.9 Pharmacokinetic Evaluations

Plasma will be collected for MEDI-563 concentration determination. The study schedule outlines when these samples will be collected. On study drug administration days (ie, Day 0 for Cohort 1 and Days 0, 28, and 56 for Cohort 2), blood samples will be drawn as follows:

Cohort 1

- Day 0: Just prior to study drug administration and 2 hours after study drug administration.

[redacted]

Cohort 2

- Day 0: Just prior to study drug administration and 2 hours after study drug administration
- Day 28: Just prior to study drug administration only
- Day 56: Just prior to study drug administration only

The requirements for sample collection, preparation, storage, and shipping are specified in the laboratory manual provided to the sites.

3.5.10 Immunogenicity Evaluations

Anti-MEDI-563 antibodies will be evaluated in serum. The study schedule outlines when these samples will be collected. The requirements for sample collection, preparation, storage, and shipping are specified in the laboratory manual provided to the sites.

3.5.11 Skin Prick Test

Skin prick testing of aeroallergens will be performed at screening to determine whether a subject is allergic. The skin prick test can be waived if it has been done previously and the subject has the results available for the study. The allergens used in the skin prick test are selected from a collection of extracts, including but not limited to cat allergen extract, short ragweed allergen extract, grass pollen or dust mite allergen extracts. Briefly, a drop of each allergen extract and the positive (histamine) and negative controls are placed on to the skin of the volar side of a forearm and pierced vertically using a 1-mm lancet or another appropriate device. After 10 minutes, the outer contour of the wheal reaction is outlined using a fine felt-tip pen, and the result is expressed as the mean of the lengths of the longest diameter and the perpendicular line through its center (Weiland et al, 2004). A skin prick test is considered positive if the mean length at 10 minutes after the skin prick is at least 2 mm larger than the size of the negative control (Weiland et al, 2004). Subjects should avoid antihistamine medications prior to the skin prick test at the discretion of the investigator based on the type of antihistamine the subject is taking.

3.5.12 Disease Evaluations

3.5.12.1 Office Spirometry

Spirometry at study sites will be performed by the investigator or qualified designee according to ATS/ERS guidelines (Miller et al, 2005) at every visit using vendor provided equipment. If a particular study visit also requires eNO, the spirometry testing needs to be completed after the eNO. Equipment, training, and a procedures manual will be provided to the site by a qualified vendor.

Prior to spirometry testing, subjects will be required to withhold the following:

- Short-acting β2-agonists for at least 8 hours

- Long-acting β2-agonists and caffeinated food products for at least 12 hours
- Leukotriene modifiers for at least 24 hours

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each office spirometry session and the 2 best efforts that meet 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. Both the absolute measurement (for FEV_1 and FVC) and the percentage of predicted normal value (Miller et al, 2005) will be recorded; the predicted value will be interpolated from an extension of the curve when the subject's values are out of range (eg, too tall or too short). 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). Nose clips will be used for office spirometry.

All sites will use standardized spirometry equipment and software provided by a qualified central spirometry vendor for protocol specified spirometry assessments. Spirometry results will be electronically transmitted to the central spirometry vendor. The equipment will be calibrated and maintained according to the central spirometry vendor's guidelines. Equipment, training, and a procedures manual will be provided to the site by the central spirometry vendor.

The vendor provided equipment should not be used when spirometry is being done as a safety assessment (ie, when inducing sputum or doing the bronchoscopy). These assessments should be performed on the site's own equipment and the results should be recorded in source documents.

3.5.12.2 Exhaled Nitric Oxide

Airway inflammation will be evaluated using a standardized single-breath eNO test (ATS, 2005). Since spirometry can potentially impact the eNO measurement, the eNO test needs be completed prior to spirometry. In addition, subjects should not eat or drink anything 1 hour prior to having the eNO test, as this may affect the results.

A seated subject inspires medical compressed air from a reservoir connected to a mouthpiece fitted with a 2-way valve. After inspiration to total lung capacity, the subject exhales immediately at a constant flow rate. The exhaled air will be collected via a side port close to the mouth and analyzed online for nitrous oxide content using an instrument calibrated with nitrous oxide gas standard. Three acceptable measurements are taken with at least 30 seconds of relaxed tidal breathing between maneuvers. The mean reading of the 3 results will be used for analysis. The nitrous oxide equipment from each study center will be calibrated per the equipment manufacturer recommendation. Equipment, training, and a procedures manual will be provided to the site by a qualified vendor.

3.5.12.3 Bronchoscopy with Airway Mucosal Biopsies

Bronchoscopies with airway mucosal biopsies are to be completed for subjects in Cohort 1 and Cohort 2 as follows:

[redacted]

Cohort 1

- Screening: Bronchoscopy with airway mucosal biopsies is to be completed 7 days (± 1 day) after screening sputum induction and within 2 days prior to Study Day 0 (Visit 1).

- Study Day 28: Bronchoscopy with airway mucosal biopsies is to be completed at least 7 days after the sputum induction and collection.

- Study Day 84 (Optional): This is optional and requires signing a separate informed consent form. Bronchoscopy with airway mucosal biopsies is to be completed at least 7 days after the sputum induction and collection.

Cohort 2

- Screening: Bronchoscopy with airway mucosal biopsies is to be completed at least 7 days after screening sputum induction and within 2 days prior to Study Day 0 (Visit 1).

- Study Day 84: Bronchoscopy with airway mucosal biopsies is to be completed at least 7 days after the sputum induction and collection.

Subjects should not have an influenza vaccine within 14 days prior to the Study Day 0 or Study Day 84 bronchoscopy. Bronchoscopies will be performed using the site's standard procedures. Spirometry will be completed prior to and after the bronchoscopy using the site's standard practice and equipment. Prior to the bronchoscopy, subjects will receive 2-4 puffs of a short-acting β2 agonist and then perform spirometry. The subject's post-bronchodilator FEV_1 should be ≥ 65% in order to proceed with the bronchoscopy. Prior to discharge, subjects should have an FEV_1 of at least 90% of the post-bronchodilator value obtained prior to performing the bronchoscopy. The investigator may administer additional short-acting β2 agonists and observe the subject as clinically indicated.

Mucosal biopsy samples should be obtained from alternating lobes of the lung. The screening mucosal biopsies should preferably be taken from the right lower lobe; the second mucosal biopsies (Study Day 28 for Cohort 1 or Study Day 84 for Cohort 2) should preferably be taken from the left lower lobe; the optional third mucosal biopsies for Cohort 1 subjects, if done (Study Day 84) should preferably be taken from the right lower lobe.

Subjects will be pretreated with an inhaled β2-agonist prior to the bronchoscopy. The decision to use anticholinergic medications (atropine or robinol), sedatives, and/or analgesics (midazolam and/or fentanyl) will be made jointly by the investigator or qualified designee, and the subject (some subjects may prefer the relaxation provided by sedatives, while others tolerate the procedures well without medication and prefer not to undergo the recovery and restrictions associated with conscious sedation). The procedure is done after local anesthesia of the upper and lower airways has been obtained using lidocaine with a dose up to 9 mg/kg or 600 mg total, whichever is less. Airway sampling includes 2-3 subsegmental and 2-3 segmental forceps endobronchial biopsies. The samples will be analyzed for eosinophils, inflammatory cells, proteins, mRNA expression, and other potential exploratory analyses depending on results.

[redacted]

Instructions for sample collection, processing, storing, and shipping will be provided in a separate laboratory manual.

3.5.12.4 Sputum Induction, Collection, and Analysis

Sputum will be induced and collected at visits described in the study schedule to better understand the effect of MEDI-563 on eosinophils in sputum samples. Reduction of eosinophils in sputum is associated with better asthma control (Green et al, 2002). The sputum sample must be completed at least 7 days before the bronchoscopies with airway mucosal biopsies unless otherwise specified in the schedule of assessments.

Prior to sputum induction, subjects will be required to withhold the following:

- Short-acting β2 agonists for at least 8 hours
- Long-acting β2 agonists and caffeinated food products for at least 12 hours
- Leukotriene modifiers for at least 24 hours

Subjects will receive 2 puffs of a short-acting β2 agonist at the site, and then spirometry will be performed 15 to 20 minutes later. If the FEV_1 is < 60%, an additional 2 puffs of a short-acting β2 agonist will be administered and repeat spirometry, using the site's standard practice and equipment, will be performed 15 to 20 minutes later. If the FEV_1 is still < 60%, then the sputum induction will need to be rescheduled. The site will need to call MedImmune to determine when the subject should return. This information should be kept in source documentation.

If the FEV_1 is ≥ 60%, the subject will inhale 3%, 4%, and 5% saline for 7 minutes each. The induction will be stopped when an adequate sample is obtained or if the subject's FEV_1 drops ≥ 20% from baseline. Samples will be aspirated in dithiothreitol and Dulbecco's phosphate buffered saline (PBS). Samples will be analyzed for inflammatory cells and other exploratory tests, such as MEDI-563 levels and inflammatory mediators. Specific procedures for collection, processing, storage, and shipping are provided in a separate study procedures manual and laboratory manual.

3.5.12.5 Bone Marrow

Subjects who sign a separate consent form for the bone marrow procedure will have bone marrow aspiration performed. Bone marrow samples will be used to better understand the mechanism of action of MEDI-563. The bone marrow procedure is optional. Subjects who do not wish to have the bone marrow biopsy done will still be eligible for the study.

The bone marrow aspirates will be analyzed for mast cells, eosinophil and basophil precursors, and mature cells. The bone marrow aspirates will be obtained from the iliac crest using a bone marrow aspiration needle. The bone marrow aspirate site will be pretreated with 2% lidocaine to numb the area. Bone marrow samples will be obtained after the area is numb (this usually takes 5 minutes after the administration of lidocaine).

For sites performing bone marrow aspirate smears, 0.5 to 1 mL of bone marrow will be obtained in a 10 mL syringe containing 1mL sterile sodium heparin (1000 units/mL).

[redacted]

For sites performing bone marrow smears and bone marrow mononuclear extraction, 4.5-10 mL of bone marrow will be obtained in a 10 mL syringe containing 1 mL sterile heparin (1000 units/mL). Samples for mononuclear extraction will be mixed on a rocker prior to processing.

Specific procedures for sample collection, processing, storage, and shipping will be provided in a separate study procedures manual and laboratory manual.

3.5.12.6 Serum and Whole Blood for Storage and Analyses

To investigate the mechanism of action of MEDI-563, serum samples and whole blood will be collected and stored for later analyses for mast cell-specific metabolites and other inflammatory mediators. Specific procedures for sample collection, processing, storage, and shipping will be provided in a separate laboratory manual.

3.5.12.7 DNA Sample Analyses

To investigate characteristics associated with subjects' clinical response and safety, 1 blood sample (8.5 mL) will be collected on Study Day 0 and frozen at –70°C for DNA sample preparation. The sample will be frozen and stored for single nucleotide polymorphism (SNP) analysis and genotyping. This will be performed by MedImmune using the Affymetrix SNP array technology. Further information on the processing of the samples is located in a separate lab manual provided to the sites by MedImmune. This will be done within the confines of the protocol.

The collection of blood for DNA analysis is optional and is not required for participation in this study. Subjects who agree to have their DNA analyzed must complete a separate informed consent form (Informed Consent Form for DNA Analysis). Further information on subject rights are included in this consent. Subjects who do not wish to have the DNA test done will still be eligible for the study.

[redacted]

[redacted]

3.5.12.10 Home Peak Flow Monitoring

Home peak flow monitoring for FEV_1 and PEF will be performed twice daily, morning and evening, by subjects from screening through End of Study/Study Termination (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2). Subjects should perform peak flow testing while sitting or standing, prior to using a short-acting β2 agonist (if needed) or other medications for their asthma. Subjects should perform peak flow testing in the same manner, either sitting or standing, throughout the study. Three tests will be performed at each time point.

Electronic devices to record peak flow measurements and diary data, as well as instructions on the use and maintenance of the devices will be provided by a qualified vendor. The electronic recording devices will be provided to each subject at screening and instructions for use will be given.

3.5.12.11 Use of Rescue Beta 2 Agonist Medication

Use of rescue β2 agonist (albuterol or equivalent) medication (total number of puffs per day) will be collected daily by the subject from screening through End of Study/Study Termination (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2) in the electronic devices provided to them at screening.

3.6 Completion of Study and Loss to Follow-up

For Cohort 1, subjects will be considered to have completed the study if they were followed up through Study Day 84. For Cohort 2, subjects will be considered to have completed the study if they were followed through Study Day 140. It should be specified on the CRF whether or not the subject completed the study through End of Study/Study Termination (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2).

Subjects will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status at Study Day 84 for Cohort 1 subjects and Study Day 140 for Cohort 2 subjects. Investigators or their qualified designees should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, follow-up should resume according to the protocol.

[redacted]

Any subject whose eosinophil count in peripheral blood is not at least 100 eosinophils/mm^3 OR has not returned to at least 70% of the baseline value at the End of Study/Study Termination (Study Day 84 for Cohort 1; Study Day 140 for Cohort 2) will be asked to return to the site every other month until the eosinophil count in peripheral blood meets one of the criteria above.

4 SAFETY ASSESSMENT

4.1 Adverse Events

4.1.1 Definition of Adverse Events

As defined by the ICH Guideline for Good Clinical Practice (CPMP/ICH/135/95), an adverse event (AE) is:

> Any untoward medical occurrence in a subject or clinical investigations subject administered a pharmaceutical product and which does not necessarily have to 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 pre-existing condition;
- An AE occurring from overdose (ie, a dose higher than that prescribed by a healthcare professional for clinical reasons, or a dose higher than that described on the marketed product label) of an investigational or marketed product, whether accidental or intentional;
- An AE occurring from abuse (eg, use for non-clinical reasons) of an investigational or marketed product;
- An AE that has been associated with the discontinuation of the use of an investigational or marketed product;
- Adverse changes from baseline that are listed on the toxicity table in Appendix A; and
- An event related to a medical procedure required by protocol prior to dosing of the study medication (protocol-related AE).

4.1.2 Study Reporting Period for Adverse Events

For Cohort 1, the reporting period for AEs is from the time the subject signs the informed consent through Study Day 84.

For Cohort 2, the reporting period for AEs is from the time the subject signs the informed consent through Study Day 140.

[redacted]

Any new sign or symptom, disease, or other untoward medical event that occurs after the subject signs the informed consent form, but before the subject has received the study drug, and which may possibly be causally related to the protocol (i.e., results from a required procedure or from withdrawal of prior medication), must be reported by the investigator as an adverse event in the same way as adverse events that occur after the subject receives study drug.

4.1.3 Recording of Adverse Events

All AEs will be recorded on the CRFs provided. Adverse events will be reported using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the study product, possible etiologies and whether the event meets criteria as a SAE and therefore requires immediate notification of the sponsor. See Section 4.2.1 for the definition of SAEs, and Section 4.3 and Section 4.4 for guidelines for assessment of severity and relationship, respectively. If the event has not resolved at the end of the study reporting period it will be documented as ongoing. If an AE evolves into a condition which becomes "serious" it will be reported on the SERIOUS ADVERSE EVENT (SAE) REPORT FORM.

4.2 Serious Adverse Events

4.2.1 Definition of Serious Adverse Events

A Serious Adverse Event (SAE) is any AE that:

- Results in death;

- Is 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 hypothetically might have caused death if it were more severe.

- 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. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent or significant disability/incapacity.
  The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect in offspring of the subject
  If the child is born with any congenital anomaly or birth defect, this should be reported to Product Safety as a SAE.

  A pregnancy should be reported to MedImmune Product Safety as an immediately reportable event (IRE; see Section 4.5). A pregnancy should be followed for outcome and the health status of the mother and the child.

- 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.

  A serious event related to a medical procedure required by protocol prior to dosing of the study medication should also be reported to Product Safety as a SAE (protocol-related SAE).

4.2.2 Study Reporting Period for Serious Adverse Events

For Cohort 1, the reporting period for SAEs is from the time the subject signs the informed consent through Study Day 84 or until eosinophil levels in peripheral blood are at least 100 eosinophils/mm^3 OR the peripheral blood eosinophil count has returned to at least 70% of the baseline value, if applicable.

For Cohort 2, the reporting period for SAEs is from the time the subject signs the informed consent through Study Day 140 or until eosinophil levels in peripheral blood are at least 100 eosinophils/mm^3 OR the peripheral blood eosinophil count has returned to at least 70% of the baseline value, if applicable.

After the initial SAE report the investigator is required to follow each subject proactively and provide further information on the subject's condition to MedImmune Product Safety.

All SAEs should be followed up to resolution by the investigator, even if this extends beyond the study reporting period. Resolution of a SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

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

4.2.3 Notification of Sponsor of Serious Adverse Events

Within 24 hours of identifying a SAE, regardless of the presumed relationship to the Study Drug, the investigator or qualified designee must complete the SAE Report form and fax to MedImmune Product Safety.

MedImmune contact information:

Product Safety
MedImmune
[redacted]

MedImmune, as sponsor of the study being conducted under an Investigational New Drug Application (IND), is responsible for reporting certain SAEs as IND safety reports to the FDA, other applicable regulatory authorities, and participating investigators, in accordance with the U.S. Code of Federal Regulations (21 CFR 312.32 and 312.33) ICH Guidelines, and/or local regulatory requirements. MedImmune may be required to report certain serious AEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by MedImmune as soon as it becomes available.

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

4.2.4 Notification of Institutional Review Board or Independent Ethics Committee of Serious Adverse Events

The investigator must comply with the applicable regulatory requirements related to the reporting of serious AEs to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB or IEC must be informed in a timely manner by the principal investigator of serious AEs occurring at their site during the study. Investigators must also submit safety information provided by MedImmune to the IRB or IEC as detailed in Section 7.2.

4.2.5 Recording of Serious Adverse Events

Serious adverse events will be recorded on the SAE REPORT FORM using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for severity, relationship to the study product, and possible etiologies. See Section 4.2.1 for the definition of SAEs, and Section 4.3 and Section 4.4 regarding guidelines for assessment of severity and relationship, respectively.

[redacted]

For the purposes of study analysis, if the event has not resolved at the end of the study reporting period it will be documented as ongoing. For purposes of regulatory safety monitoring the investigator is required to follow the event to resolution and report to the sponsor the outcome of the event using the SAE REPORT FORM.

4.3 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 a health care professional who is qualified to review AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment and the severity categories of Mild, Moderate, and Severe provided below, and in the toxicity table (Appendix A).

Another consideration to assist investigators in distinguishing between the severity levels would include the level of medical intervention required in response to the AE. For example, in general, an event of mild severity may include symptomatic over the counter treatment managed by the subject. An event of moderate severity may require generally symptomatic medical intervention by a health care professional. In contrast, a severe event might require more immediate medical evaluation and intervention by a health care professional.

1. Mild: Mild level of discomfort and does not interfere with regular activities

2. Moderate: Moderate level of discomfort and significantly interferes with regular activities

3. Severe: Significant level of discomfort and prevents regular activities

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.2.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be a SAE.

4.4 Assessment of Relationship

An AE is considered “product-related” for the purposes of regulatory reporting if the investigator, the medical monitor, or the product safety physician assesses the AE as possibly, probably, or definitely related to study drug. This is not a conclusive determination of causal association between the product and the event.

Whenever the investigator’s assessment is unknown or unclear, the AE is treated as product-related for the purposes of reporting to regulatory authorities. An AE may be deemed to be not related to the product for purposes of regulatory reporting only if the investigator, medical monitor, and product safety physician, if applicable, agree that the AE is not product-related

The investigator is required to provide an assessment of relationship of AEs and serious AEs to the study product. A number of factors should be considered in making this assessment

including: 1) the temporal relationship of the event to the administration of study product; 2) whether an alternative etiology has been identified; and 3) biological plausibility. The following guidelines should be used by investigators to assess the relationship of an AE to study product administration.

Relationship assessments that indicate an **"Unlikely Relationship"** to study product:

None: The event is related to an etiology other than the study product (the alternative etiology must be documented in the study subject's medical record).

Remote: The event is unlikely to be related to the study product and likely to be related to factors other than study product.

Relationship assessments that indicate a **"Likely Relationship"** to study product:

Possible: There is an association between the event and the administration of the study product and there is a plausible mechanism for the event to be related to study product; but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.

Probable: There is an association between the event and the administration of study product, a plausible mechanism for the event to be related to the study product and the event could not be reasonably explained by known characteristics of the subject's clinical status or an alternative etiology is not apparent.

Definite: There is an association between the event and the administration of study product, a plausible mechanism for the event to be related to the study product and causes other than the study product have been ruled out and/or the event re-appeared on re-exposure to the study product.

4.5 Other Events Requiring Immediate Reporting

The following events must be reported ***within 24 hours*** by fax to MedImmune Product Safety using the fax notification form:

1. Any withdrawal of consent during the study
2. Pregnancy or intent to become pregnant*
3. Infusion reaction (Cohort 1)
4. Anaphylactic reaction (defined in Section 4.9)

*Subjects who become pregnant during the study period must not receive additional doses of study product but will be followed on study. A pregnancy should be followed for outcome, any premature terminations reported, and the health status of the mother and child including date of delivery and the child's gender and weight should be reported to MedImmune Product Safety after delivery.

[redacted]

4.6 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 immediate review of SAEs and timely review of other AEs reported during the study. MedImmune Product Safety is responsible for the receipt, immediate medical/clinical review, investigation, and follow-up of SAEs reported from the clinical study sites.

The SMC will independently review cumulative safety surveillance data on a regular basis throughout the study and make recommendations regarding further conduct of the study. The SMC will also review safety data at other time points in response to AEs felt to be medically significant by the medical monitor. The SMC is composed of at least 2 MedImmune physicians who are not directly involved in the day to day operations of the study, and at least 2 physicians who are not employees of MedImmune.

The SMC will review blinded safety surveillance data reported to MedImmune, but may request to be unblinded if necessary to make safety assessments and study recommendations.

4.7 Interruption or Discontinuation of Study Dosing in Individual Subjects

Individual subjects in Cohort 2 will not receive further study drug if any of the following occur in the subject in question:

1. Withdrawal of consent
2. Pregnancy
3. Any anaphylactic event (defined in Section 4.9) or serious allergic event related (possibly, probably, or definitely) to the study drug
4. Any SAE judged possibly, probably, or definitely related to study drug
5. The occurrence of immune complex disease
6. Event which in the opinion of the investigator contraindicates further dosing such as illnesses or complications

Subjects who discontinue prematurely will return to the study site to complete the study discontinuation visit as defined in the protocol. After the study discontinuation visit, subjects will be followed for the full study period (through Study Day 84 or Study Day 140, as appropriate) for safety evaluations only (including CBC with differentials and platelets, serum chemistry, urinalysis, ECG, and anti-MEDI-563 antibodies) and MEDI-563 plasma levels, as defined in the schedule of evaluations, unless consent for follow-up is withdrawn.

4.8 Interruption or Discontinuation of Study Dosing and Randomization

If any of the following occur, no further administration of study drug will take place and no other subjects will be randomized into the study, until after review of the event in question by the medical monitor and the SMC:

1. Death from any cause in any subject judged related to study drug

[redacted]

2. Any anaphylactic event or 2 serious allergic events related to study drug
3. Two medically similar SAEs related to study drug in the same dose cohort
4. The occurrence of immune complex disease
5. Events that, in the opinion of the medical monitor and SMC, contraindicate further dosing of additional subjects.

If one of the above-listed events occurs, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted by the medical monitor and the SMC to determine whether dosing and study entry should be resumed, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the SMC are required for resumption of the study in the event the study is interrupted because of one of the above-listed events.

4.9 Monitoring of Dose Administration

Vital signs will be monitored before and after study drug administration.

As with any monoclonal antibody, non-IgE mediated infusion reactions or allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute hypotensive, bronchoconstrictive, or anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat these reactions.

Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death (Sampson et al, 2006). 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

2. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
3. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).
4. 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).

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

5 STATISTICAL CONSIDERATIONS

5.1 General Considerations

The analysis of study data is the responsibility of MedImmune or its designee. A comprehensive statistical analysis plan will be developed and approved prior to the database lock.

All data will be provided in data listings sorted by dose cohort, treatment groups (MEDI-563 or placebo), and visit number. Summary data will be presented in tabular format by cohort and treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics including N, mean, standard deviation, median, and range.

5.2 Interim Analysis

An interim analysis will be conducted after second biopsy results from Cohort 1 are available. All safety data available at this time will be included in the interim analyses. Additional analyses on PK and PD data may be performed to help make decisions on dose selection for future studies.

To ensure the blinding of each subject's treatment assignment throughout the study, the interim analysis will be performed by programmers and statisticians who are not involved in the conduct of this study. A limited number of MedImmune personnel who will analyze airway biopsy results, and PK and PD data, will be unblinded during the conduct of the study. Except for the personnel described in Section 3.2.2 (Blinding), MedImmune, and study site personnel associated with this study as well as the subjects will remain blinded to the treatment assignment for individual subjects until the last subject completes Study Day 84 (Cohort 1) or Study Day 140 (Cohort 2) and the database is locked. Summaries of interim analyses results will be reviewed by MedImmune senior management. The individual treatment code may be made available to these reviewers, if necessary.

5.3 Sample Size

A total of up to 24 subjects will participate in this study, with 12 subjects randomized to receive either MEDI-563 or placebo in a 2:1 ratio for Cohort 1 (an additional 3 subjects per cohort may be randomized if eligible subjects are in screening at the time 12 subjects are randomized); and 12 subjects randomized to receive either MEDI-563 (100 mg or 200 mg) or placebo in a 1:1:1 ratio for Cohort 2 (an additional 3 subjects may be randomized in if eligible subjects are in screening at the time 12 subjects are randomized). The placebo group will be included in the study to measure potential placebo effect in this population. Since there is no data available for airway mucosal biopsies in subjects treated with MEDI-563, formal sample size calculation is

[redacted]

not carried out for the primary endpoint (ie, percent change from baseline in eosinophil counts in airway mucosal biopsies). Therefore, sample size is based on clinical judgment.

Table 6 and Table 7 present the probability of observing at least one subject with an infrequently occurring AE when assuming a range of potential observed event rates and exact binomial 95% confidence intervals to assess the precision of estimates of the AE rate for MEDI-563.

Table 6 Expected Number of Subjects with AEs and Probabilities of Observing at Least 1 or 2 Subjects with AEs Given the True Event Rates

N	True Event Rate (%)	Number of Subjects with AEs Expected	Probability of Observing at least One Subjects with an AE (%)	Probability of Observing at least 2 Subjects with AEs (%)
4	2.5	0	9.6	0.4
4	5	0	18.5	1.4
8	2.5	0	18.3	1.6
8	5	0	33.7	5.7
12	2.5	0	26.2	3.5
12	5	1	46.0	11.8
16	2.5	0	33.3	5.9
16	5	1	56.0	18.9

Table 7 Estimated AE Rates and 95% Exact Binomial Confidence Intervals Given the Number of Subjects with AEs Observed

N	Number of Subjects with AEs Observed	Estimated Event Rate (%)	95% Confidence Interval %
4	0	0.0	(0.00, 60.24)
4	1	25	(0.63, 80.59)
8	0	0	(0.00, 36.94)
8	1	12.5	(0.32, 52.65)
12	0	0	(0.00, 26.46)
12	1	8.3	(0.21, 38.48)
16	0	0	(0.00, 20.59)
16	1	6.25	(0.16, 30.23)

Table 8 shows the probabilities of observing sample mean of percent change from baseline in eosinophil counts in airway mucosal biopsies are more than 80% or 60% under the assumption that percent change from baseline is normal, $N(\gamma,\sigma^2)$ with sample SD = 0.4, 0.6, 0.8 and γ = 0.9, 0.8, 0.7, 0.6, 0.5.

Table 8 Probability of Observing the Point Estimate of the Percent Change from Baseline ≥ 80% or 60% in Eosinophil Counts in Airway Mucosal Biopsies

N	True % Change From Baseline	Estimated Standard Deviation	Probability of Observing ≥ 80% Change from Baseline	Probability of Observing ≥ 60% Change from Baseline

[redacted]

N	True % Change From Baseline	Estimated Standard Deviation	Probability of Observing ≥ 80% Change from Baseline	Probability of Observing ≥ 60% Change from Baseline
8	0.900	0.4	0.75	0.96
8	0.800	0.4	0.50	0.90
8	0.700	0.4	0.25	0.75
8	0.600	0.4	0.10	0.50
8	0.500	0.4	0.04	0.25
8	0.900	0.6	0.67	0.90
8	0.800	0.6	0.50	0.81
8	0.700	0.6	0.33	0.67
8	0.600	0.6	0.19	0.50
8	0.500	0.6	0.10	0.33
8	0.900	0.8	0.63	0.84
8	0.800	0.8	0.50	0.75
8	0.700	0.8	0.37	0.63
8	0.600	0.8	0.25	0.50
8	0.500	0.8	0.16	0.37

5.4 Subject Populations

Three subject populations, Intent to Treat (ITT) population, According to Protocol (ATP) population, and Safety population, will be considered in this study.

ITT Population

The ITT population will include all subjects who have been randomized into the study.

ATP Population

The ATP population is described below by Cohort

Cohort 1 subjects who meet the following criteria will be included in the ATP population:

- Receive investigational product (MEDI-563 or placebo), and
- Have airway mucosal biopsy results at screening and Study Day 28, and
- Do not receive a burst of corticosteroids (oral, injectable, IV) within 28 days prior to the second airway biopsy (Study Day 28)

Cohort 2 subjects who meet the following criteria will be included in the ATP population:

- Receive 3 doses of investigational product (MEDI-563 or placebo), and
- Have airway mucosal biopsy results at screening and Study Day 84, and
- Do not receive a burst of corticosteroids (oral, injectable, IV) within 28 days prior to the second airway biopsy (Study Day 84), and

[redacted]

- Do not contract an upper or lower respiratory infection requiring antibiotics or antivirals within 28 days prior to the second airway biopsy (Study Day 84)

Safety Population

The safety population will include all subjects who receive study drug. All safety analyses will be based on the safety population.

5.5 Primary Endpoints

The primary objectives of this study are to evaluate the safety and tolerability and to evaluate the effects of MEDI-563 on airway mucosal eosinophils 28 days after completion of dosing in adults with asthma. Adverse events will be described by system organ class (SOC), severity, and relationship to study drug through Study Day 84 (Cohort 1) or through Study Day 140 (Cohort 2). Serious adverse events will be described by SOC, severity, and relationship to study drug through Study Day 84 (Cohort 1), through Study Day 140 (Cohort 2), or through the end of long-term follow-up, if applicable. As safety assessments, NK cell counts, serum CRP, ECP, EDN, IL-5, IL-6, and tryptase levels, and ECG will be evaluated in the MEDI-563 and placebo groups as changes from baseline. Percent change from baseline in eosinophil counts in the airway mucosa (on Study Day 28 for Cohort 1 or on Study Day 84 for Cohort 2) will be summarized by cohort, treatment group, and visit.

5.6 Secondary Endpoints

The secondary objectives of this study are to evaluate the PK and IM of MEDI-563. Plasma MEDI-563 concentration data will be tabulated by cohort together with descriptive statistics. Individual and mean plasma concentration-time profiles of MEDI-563 by dose cohort will be generated. Noncompartmental PK data analysis of plasma concentrations of MEDI-563 will be performed using the software package WinNonlin®. The noncompartmental pharmacokinetic parameters to be obtained and reported include, but are not limited to: the C_{max}, AUC, terminal elimination half-life ($t_{1/2}$) and systemic clearance (CL) if the data allows. For Cohort 2 subjects, C_{max} and pre-dose trough (C_{min}) plasma concentrations will be summarized following each dose. Descriptive statistics of these noncompartmental parameters by dose cohort will also be provided. Immunogenicity results will be listed for all subjects and the percentage of subjects who developed detectable anti-MEDI-563 antibodies will be calculated and reported.

5.7 Exploratory Endpoints

Exploratory endpoints may include FEV_1, FVC, peak morning flow, ACQ, use of rescue β2 agonist medication, AQLQ(S) sputum inflammatory cells, number of bone marrow eosinophils and eosinophil precursors, serum levels of eosinophil- and basophil-derived proteins and inflammatory cytokines, cells in airway mucosal biopsies, downstream effects of MEDI-563 on mRNA levels in whole blood, and exploration of single-nucleotide-polymorphisms and microsatellite or short tandem repeat analyses in whole blood DNA. All these endpoints and corresponding change from baseline will be summarized by cohort and treatment group.

[redacted]

6 DATA COLLECTION AND 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 considered the source documents for the purposes of auditing the study.

Data recorded on source documents will be transcribed onto a validated data collection method provided by MedImmune or designee. Collected data will be reviewed by the sponsor or designee, with a copy retained by the investigator.

The study will be monitored by MedImmune or its designee on a regular basis throughout the study period. All study documents (subject files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be maintained in a secure place for a period of 2 years following marketing of MEDI-563 or for 2 years after centers have been notified that the IND has been discontinued. There may be other circumstances for which MedImmune is required to maintain study records and, therefore, MedImmune should be contacted prior to removing study records for any reason.

7 HUMAN SUBJECTS

7.1 Ethics and Regulatory Considerations

The study will be conducted according to the Declaration of Helsinki, Protection of Human Subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

The protocol will be reviewed and approved by the IRB or IEC of each participating center prior to study initiation. Serious AEs regardless of causality will be reported to the sponsor and to the IRB/IEC, and the investigator will keep the IRB/IEC informed as to the progress of the study.

The investigator or qualified designee will explain the nature of the study and will inform the subject that participation is voluntary and that they can withdraw at any time. Written informed consent will be obtained from each subject prior to entry into the study. A copy of the signed consent form will be given to every participant and the original will be maintained with the subject's records.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a subject's name to a subject identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA, the sponsor, or its agents, of the clinical trial. The principal investigator must also comply with all applicable privacy regulations (e.g. Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

7.2 Institutional Review Board or Independent Ethics Committee

A list of IRB/IEC members should be obtained by the investigator and provided to the sponsor.

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

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

The IRB/IEC must be informed by the principal investigator of informed consent changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study; 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.

7.3 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki should be implemented before any protocol-specified procedures or interventions are carried out. Informed consent will be obtained in accordance with 21 CFR 50.25.

Information should be given in both oral and written form, and subjects must be given ample opportunity to inquire about details of the study.

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Subjects must be informed about the aims, expected benefits, possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or the fetus, if the subject should become pregnant) which are currently unforeseeable. They must also be informed of alternative procedures. Subjects must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. They must be informed whom to contact for answers to any questions relating to the research project. The subjects must be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time, without penalty or loss of benefits to which they are otherwise entitled. The extent of the confidentiality of subject records must be defined, and subjects must be informed

that applicable data protection legislation will be complied with. Subjects must be informed that the monitor(s), auditor(s), IRB/IEC members, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject is authorizing such access.

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

8 STUDY COMPLETION

All materials or supplies provided by the sponsor will be returned to the sponsor upon study completion. The investigator will notify the IRB/IEC when the study has been completed.

9 PUBLICATIONS

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

10 CHANGES IN THE PROTOCOL

The protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory agencies and IRBs/IECs, and must be approved by the IRB/IEC prior to their implementation. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Protocol Version 1.1 [redacted] was amended to Protocol Version 2.0 on [redacted].
Protocol Version 2.0 was amended to Protocol Version 3.0 on [redacted].
Protocol Version 3.0 was amended to Protocol Version 4.0 on [redacted].
Protocol Version 4.0 was amended to Protocol Version 5.0 on [redacted].
Protocol Version 5.0 was amended to Protocol Version 6.0 on [redacted].
Protocol Version 6.0 was amended to Protocol Version 7.0 on [redacted].

Changes to the protocol are described in Appendix E.

[redacted]

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APPENDIX A Toxicity Table (Adverse Event Grading Table)

	SEVERITY		
	Mild	Moderate	Severe
CLINICAL FINDINGS			
Injection Site Reactions			
Pain at Injection Site	Painful to touch	Painful when moved	Severe pain at rest
Redness at Injection Site	> 0 – ≤ 2 inch max diameter	> 2 – ≤ 3 inch max diameter	> 3 inch max diameter
Swelling at Injection Site	> 0 – ≤ 2 inch max diameter	> 2 – ≤ 3 inch max diameter	> 3 inch max diameter
LABORATORY VALUES			
Hematologic			
Hemoglobin (mg/L)	10.0 – 11.0 × 10^4 mg/L	8.0 – < 10.0 × 10^4 mg/L	< 8.0 × 10^4 mg/L
WBC Increased (cells/µL)	11,000 – 15,000 cells/µL	> 15,000 – 20,000 cells/µL	> 20,000 cells/µL
WBC Decreased (cells/µL)	2,700 – 3,700 cells/µL	1,700 – < 2,700 cells/µL	< 1,700 cells/µL
Lymphocytes Decreased (cells/µL)	750 – 1,000 cells/µL	500 – < 750 cells/µL	< 500 cells/µL
Neutrophils Decreased (cells/µL)	1,000 – 1,500 cells/µL	750 – < 1,000 cells/µL	< 750 cells/µL
Platelets Decreased (cells/µL)	75,000 – 125,000 cells/µL	50,000 – < 75,000 cells/µL	< 50,000 cells/µL
Liver			
Transaminases (AST/ALT)	1.50 – 2.50 × ULN	> 2.50 – 3.50 × ULN	> 3.50 × ULN
Pancreas			
Amylase	1.50 – 2.50 × ULN	> 2.50 – 3.50 × ULN	> 3.50 × ULN
Lipase	1.50 – 2.50 × ULN	> 2.50 – 3.50 × ULN	> 3.50 × ULN
Renal			
Serum Creatinine	1.25 – 1.50 × ULN	> 1.50 – 3.00 × ULN	> 3.00 × ULN
BUN	1.25 – 1.50 × ULN	> 1.50 – 3.00 × ULN	> 3.00 × ULN
Urinalysis			
Proteinuria	1+	2 – 3+	4+
Hematuria	Micro only (> 5 cells/HPF)	Gross; no clots	Gross; + clots
Other			
Sodium (mEq/L) Hypernatremia Hyponatremia	 > ULN – 150 mEq/L < LLN – 130 mEq/L	 > 150 – 155 mEq/L < 130 – 120 mEq/L	 > 155 mEq/L < 120 mEq/L
Potassium (mEq/L) Hyperkalemia Hypokalemia	 > ULN – 5.5 mEq/L < LLN – 3.0 mEq/L	 > 5.5 – 6.0 mEq/L < 3.0 – 2.5 mEq/L	 > 6.0 mEq/L < 2.5 mEq/L
Chloride (mEq/L) Hyperchloremia Hypochloremia	 > ULN – 115 mEq/L < LLN – 85 mEq/L	 > 115 – 120 mEq/L < 85 – 80 mEq/L	 > 120 mEq/L < 80 mEq/L
Bicarbonate (mEq/L)	< LLN – 16 mEq/L	> 10 – 16 mEq/L	≤ 10 mEq/L
Glucose (mg/dL) Hyperglycemia Hypoglycemia	 > ULN – 160 mg/dL < LLN – 55 mg/dL	 > 160 – 250 mg/dL 40 – < 55 mg/dL	 > 250 mg/dL < 40 mg/dL
ULN = Upper limit of normal; LLN = Lower limit of normal; HPF = High-power field			

[redacted] [redacted]

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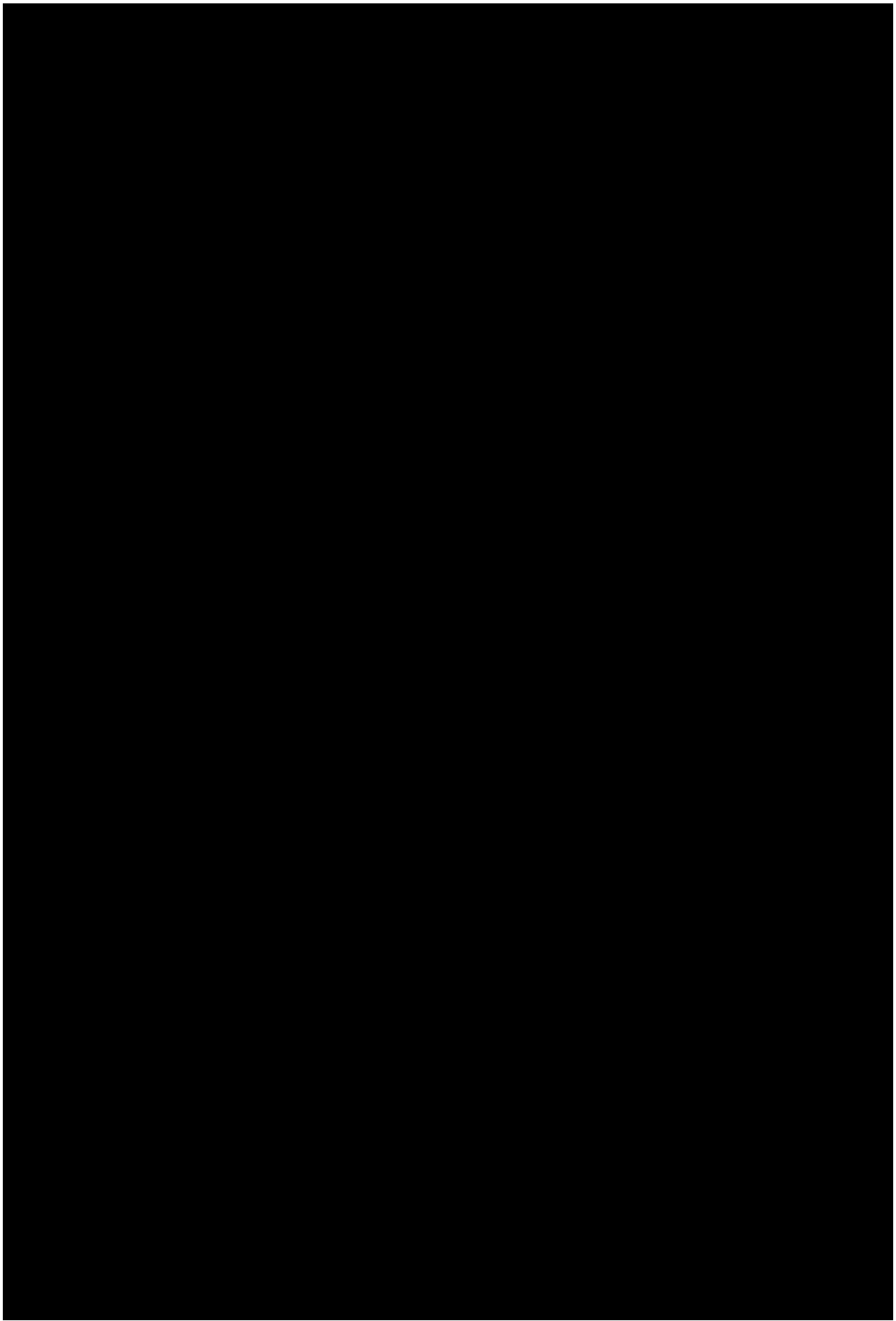

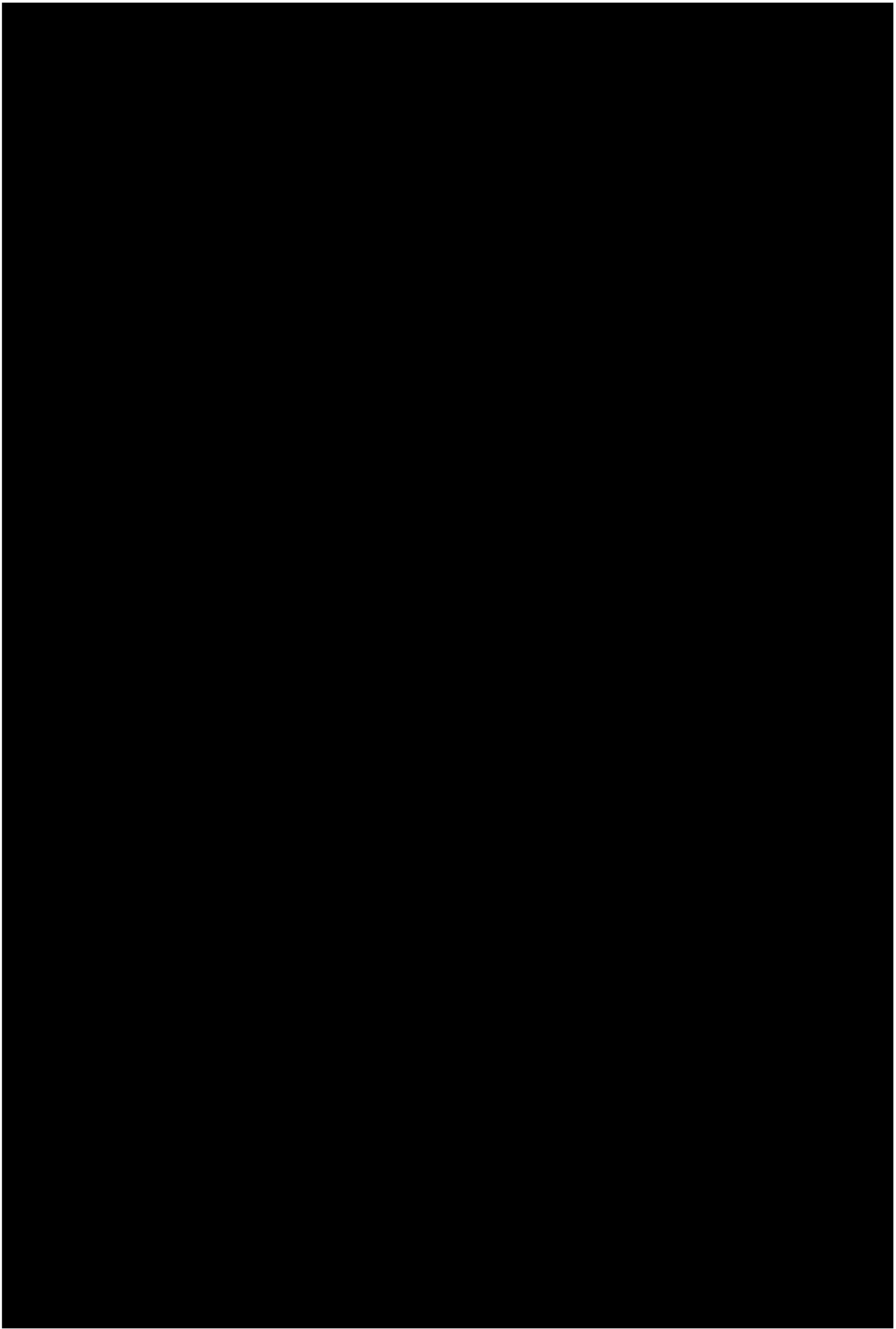

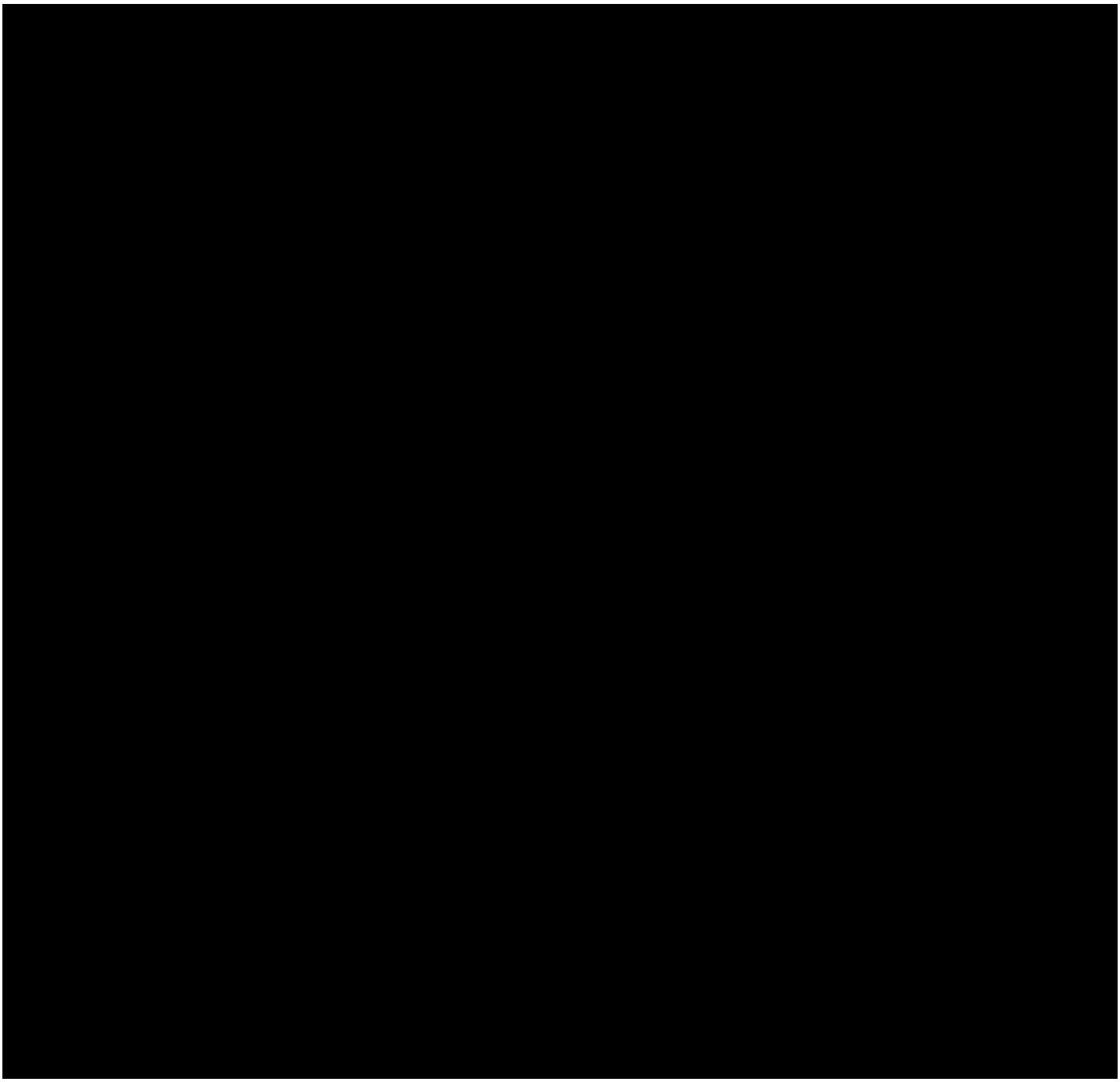

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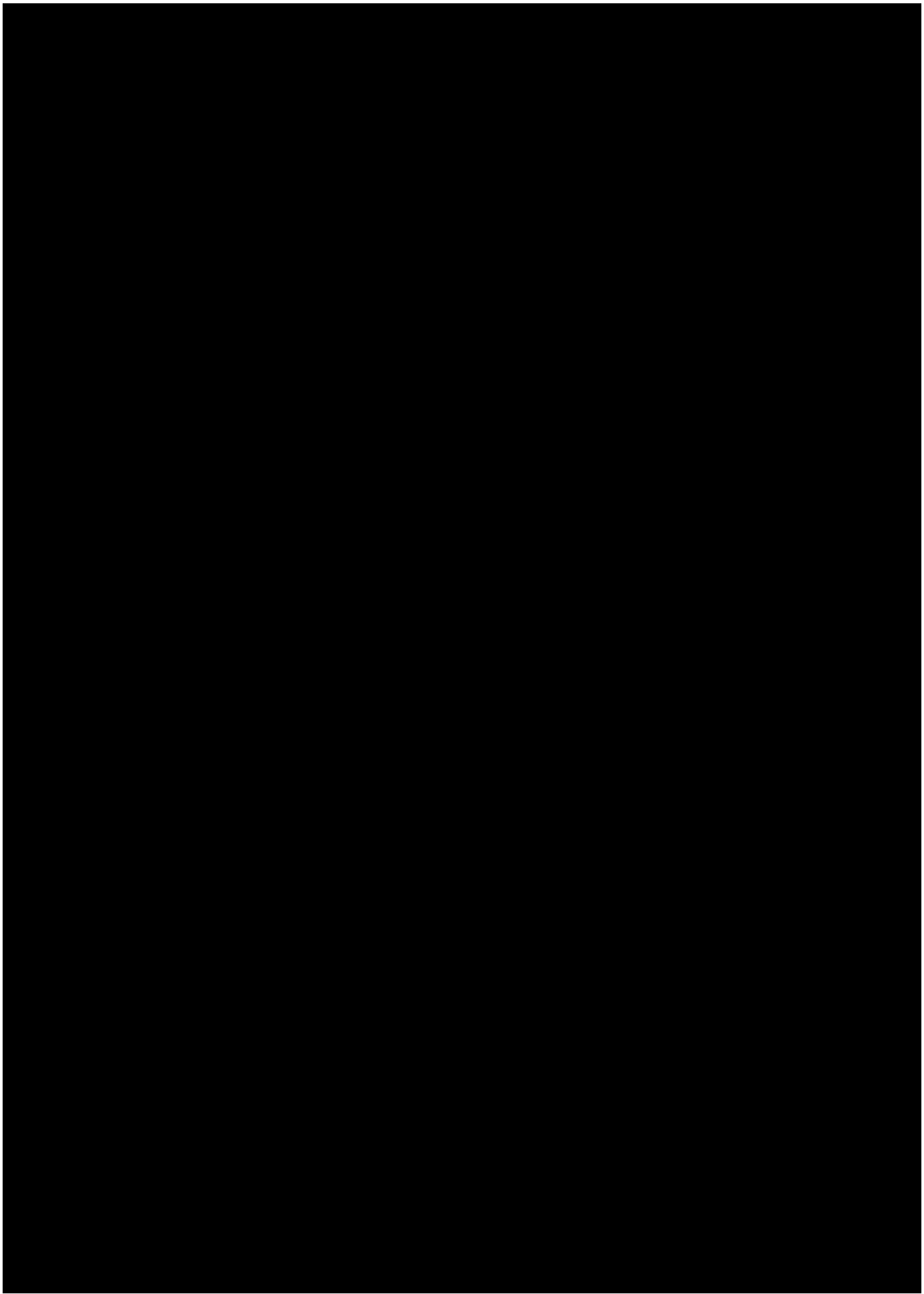

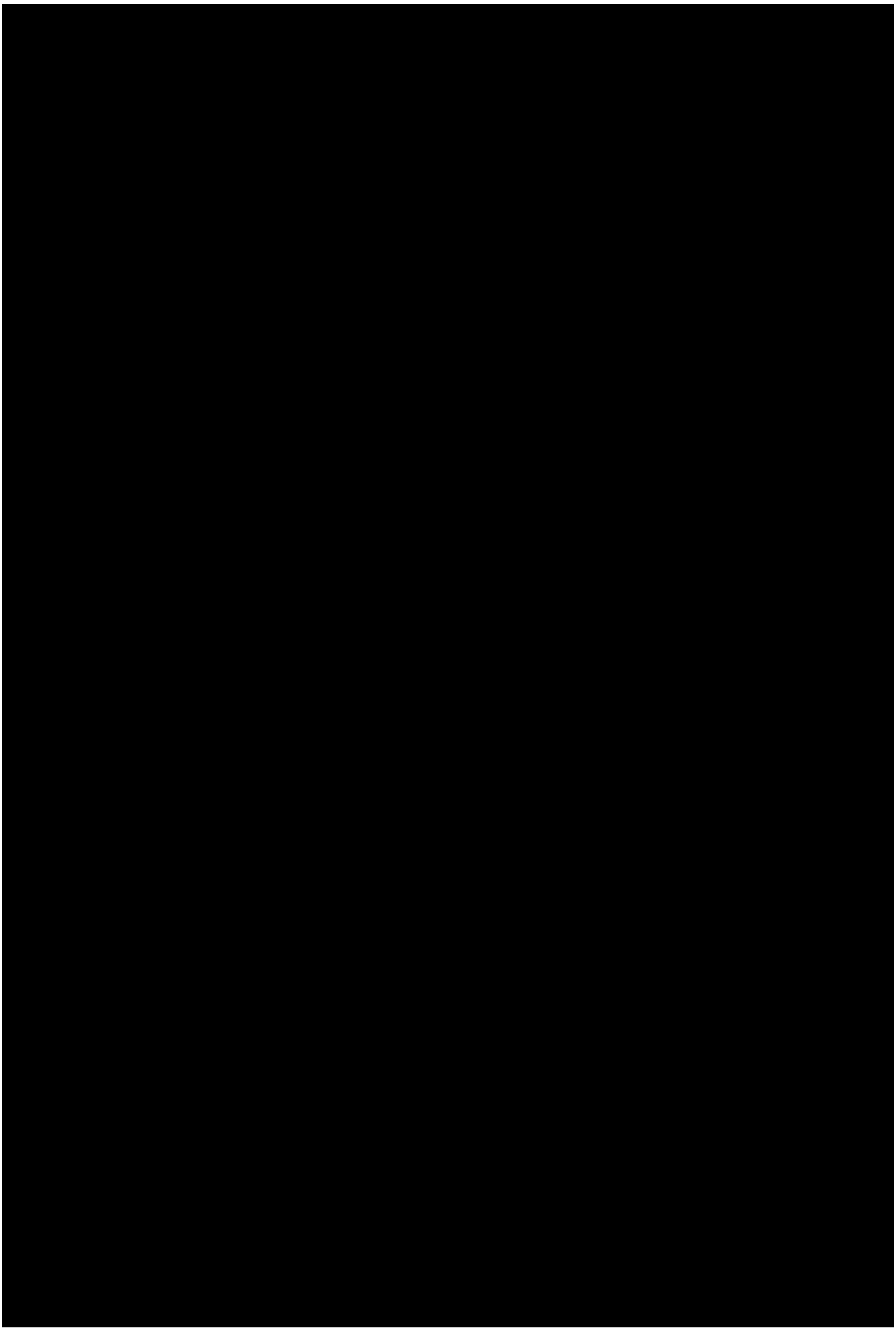

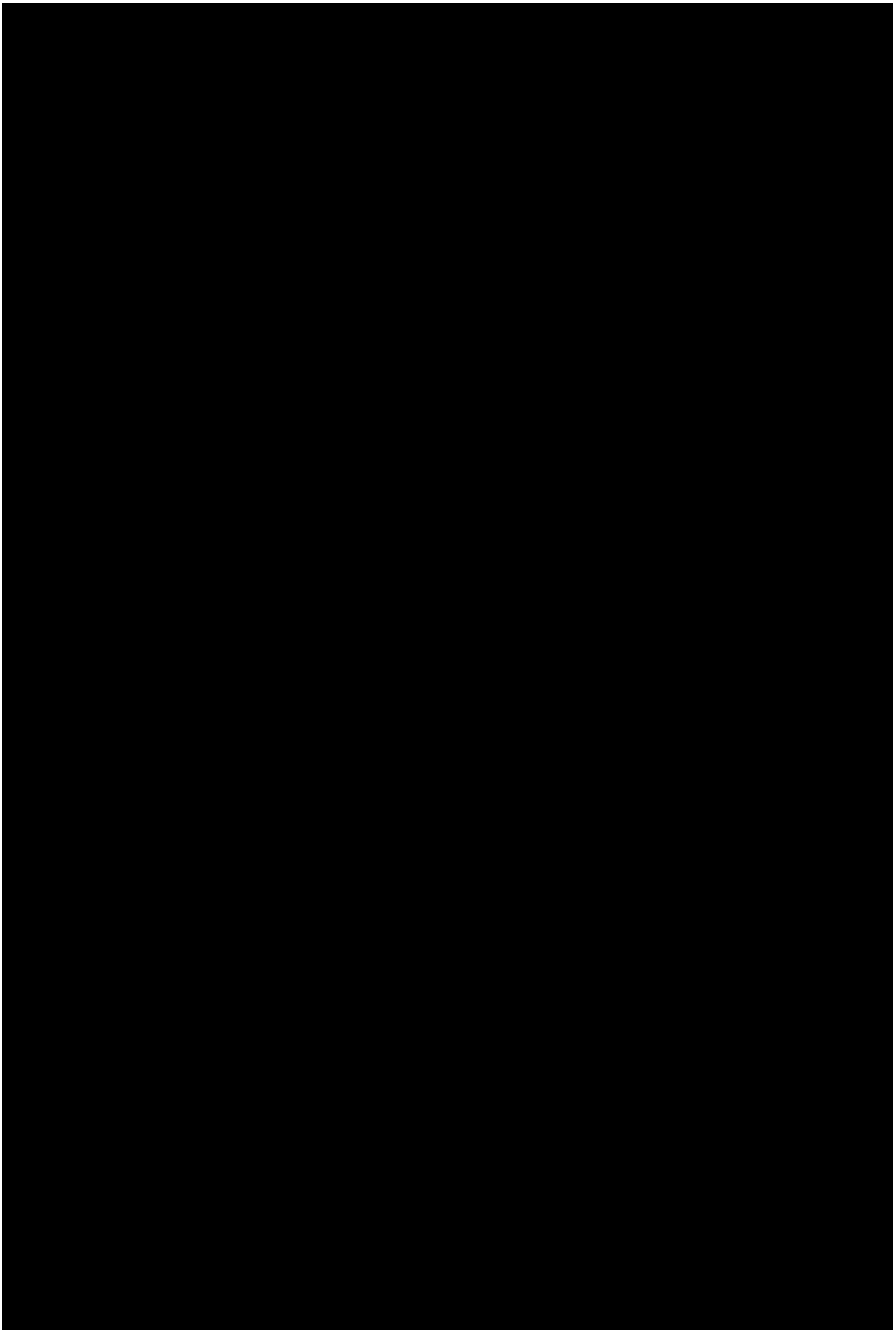

APPENDIX D Age-adjusted Lower Limit of Normal for FEV_1/FVC Ratios (2007 NHBLI Asthma Guidelines)

FIGURE 4–6. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

— Assessing severity and initiating treatment for patients who are not currently taking long-term control medications

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Treatment (See figure 4–5 for treatment steps.)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

—

Key: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Guidelines for the Diagnosis and Management of Asthma: Expert Panel Report 3. 2007. Bethesda, MD: NIH publication no. 08-4051. August 2007. Page 344.

APPENDIX E Summary of Amendments to the Protocol

Protocol Version 2.0, [redacted]

All text revisions resulting from this amendment are incorporated in the body of Protocol Version 2.0. Major changes tot he protocol are described below.

1. MedImmune Inc. was changed to MedImmune throughout the document. This change was made because MedImmune is no longer incorporated.

2. The study monitor was changed from [redacted], [redacted] to MedImmune. [redacted] is providing contract monitors to MedImmune, thus MedImmune is responsible for the study monitoring.

3. Patient identification number (PID) was changed to participant identification number (PID) throughout the document. Patient identification number was incorrect.

4. Section 3.1.2 (Exclusion Criteria): Exclusion criterion #5 was revised. Original text allowed inhaled corticosteroids if the dose was ≤800 µg/day. The text was changed to allow inhaled corticosteroids if the dose is ≤800 µg/day **budesonide (or another ICS of equivalent dose)**. This change was made to clarify the dose of ICS. Given the differences in potency of inhaled corticosteroids, ≤800 µg/day could be a high dose for some and a low dose for others.

5. Section 3.3.5 (Restricted Medications): The asterisk in this section was changed from: ***~~The dose of ICS must be constant and not more than 800 µg~~** to: ***If the subject is receiving ICS, the dose should be ≤ 800 µg/day of budesonide or an equivalent dose of another ICS. The ICS dose equivalence is established on the basis of National Asthma Education and Prevention Program criterion (National Heart, Lung, and Blood Institute [NHLBI], 2007). This change clarifies the intensity of doses between products.**

6. Section 3.4 Table 5 (Study Schedule for Single-dose Part of the Study): Study Day 77 was revised to include: Record concomitant medications, assess AEs/SAEs; collect subject home peak flow monitoring, use of rescue β2 agonists, and the ACQ. These changes were made so that Single-dose Study Day 77 assessments and Multiple-dose Study Day 140 assessments are the same.

7. Section 3.4.1 (Study Procedures for Single-dose Cohorts 1-4): The urine drug test was removed from screening. There was no urine drug test in this study.

   Study Day 77 was revised to include the ACQ, Record any changes to concomitant medications, assess AEs and SAEs, and collect subject's daily home peak flow results and rescue β2 agonist use. These changes were made so that the Single-dose Study Day 77 assessments and Multiple-dose Study Day 140 assessments are the same.

8. Section 3.5.8 (Pharmacokinetic Evaluations): Text was revised to correspond with the schedule of events. Blood samples will be collected at designated visits, not every visit. Text was changed for clarification.

9. References: The full reference for NHLBI, 2007 was added to the references because it was included in Section 3.3.5.

[redacted]

Protocol Version 3.0, [redacted]

All text revisions resulting from this amendment are incorporated in the body of Protocol Version 3.0. Major changes to the protocol are described below.

1. Atopic asthma was changed to asthma in the title of the protocol and throughout the document. This change was made because atopy is being removed from the inclusion criteria.

2. The medical monitor was changed from [redacted]

3. Section 2.2 and throughout the protocol, the pharmacodynamics (PD) of MEDI-563 was removed as a secondary endpoint. Pharmacodynamic endpoints are assessed as part of the exploratory endpoints in this study.

4. Section 3.1.1, inclusion criterion #3 was modified to allow proof of a methacholine challenge as a basis for the diagnosis of asthma (PC_{20} < 8 mg/ml).

5. Section 3.1.1, inclusion criterion #5 was modified. FEV1/FVC was changed from ≤ 70% to ≤ 75% and predicted was removed

6. Section 3.1.1, inclusion criterion #6 was modified and language in the protocol was changed to subjects must have **≥ 2.5%** ~~**≥ 3.0%**~~ eosinophils in sputum to be included in the study. This criterion was changed to increase enrollment in the study.

7. Section 3.1.1, inclusion criterion #7 was removed. A positive skin prick test (or positive history) to aeroallergens is no longer required for enrollment. Subjects who do not have atopic asthma are to be included in the study to increase enrollment.

8. Section 3.1.2, exclusion criterion #4 was removed. Subjects with aspirin related or non-steroidal anti-inflammatory drug-related asthma are no longer excluded from participating in the study. People with aspirin related asthma may have high amounts of eosinophils in sputum. As such, these subjects should be included in the study.

9. Section 3.1.2, exclusion criterion #5, and Section 3.3.5 (Restricted Medications) of the protocol were changed. Inhaled corticosteroids are allowed at any dose, as long as the subject is on a stable dose for at least 4 weeks prior to Study Day 0 and remains on a stable dose until after the first follow-up bronchoscopy (Study Day 28 for single-dose administration; Study Day 91 for multiple-dose administration). This criterion was change from dose of ICS being ≤ 800 µg/day of budesonide or an equivalent dose of another ICS, to increase enrollment in the study.

10. Section 3.4, Table 5 (Study Schedule) was changed as follows:

    - The height measurement was removed from Study Day 0. Height will only be collected one time as part of the screening physical examination.
    - The skin prick test was moved from eligibility section to disease activity, as a positive skin prick test is no longer part of the inclusion criteria.

[redacted]

- Record concomitant medications, assess AEs/SAEs, and collect subject's daily home peak flow results and rescue β2 agonist use were added to Study Day 21, because and the concomitant medications, assessment of AE/SAEs, and home monitoring are part of the Study Day 21 assessments.
- The PK/PD section was changed to PK/IM and anti-MEDI-563 antibodies were moved to this section. The PD assessments are included in other parts of the table.
- The first footnote (a) was changed to remove Study Day 21, 42, and 63, as subjects only receive study drug on Study Day 0.

11. Section 3.3.2. (Treatment Regimens) was changed to add the following to: single-dose administration: **All infusions must be administered with a 0.22 µm protein-sparing/low in-line filter, which will be supplied by the sponsor. All doses, except the 0.003 mg/kg dose, must be administered over at least 30 minutes. The 0.003 mg/kg dose must be administered over at least 5 minutes, and sites may use an infusion pump**, and to multiple-dose administration: **All infusions must be administered with a 0.22 µm protein-sparing/low in-line filter, which will be supplied by the sponsor. All doses must be administered over at least 30 minutes and sites may use an infusion pump.** This was added for consistency with the study drug administration section.

12. Section 3.4, Table 6 (Study Schedule) was changed as follows:

    - The height measurement was removed from Study Day 0. Height will only be collected one time as part of the screening physical examination.
    - The skin prick test was moved from eligibility section to disease activity, as a positive skin prick test is no longer part of the inclusion criteria.
    - The PK/PD section was changed to PK/IM and anti-MEDI-563 antibodies were moved to this section. The PD assessments are included in other parts of the table.

13. Section 3.4.1 (Study Procedures for Single-dose Cohorts 1-4) Study Day 21, bullets were added for record any changes to concomitant medications, assess AEs/SAEs, and collect subject's daily home peak flow results and rescue β2 agonist use, to be consistent with multiple-dose study procedures. The ECG was removed from Study Day 56 for consistency with the study schedule.

14. Section 3.4.2 (Study Procedures for Multiple-dose Cohorts 2-4) Study Day 42 and Study Day 63, a bullet was added for MEDI-563 plasma concentration. This change was made for consistency with Section 3.5.8 (Pharmacokinetic Evaluations). When study drug is administered (Study Day 0 for all subjects, and Study Day 21, Day 42, and Day 63 for multiple-dose subjects), blood samples will be drawn just prior to study drug administration and 2 hours after study drug administration for PK analyses.

15. Section 3.5.11.2, (eNO) was changed to add: **In addition, subjects should not eat or drink anything 1 hour prior to having the eNO test, as this may affect the results.**

16. Section 3.5.11.3 (Bronchoscopy with airway mucosal biopsies) was modified to add the following text: **Mucosal biopsy samples should be obtained from alternating lobes of the lung. The screening mucosal biopsy should preferably be taken from the right**

lower lobe; the second mucosal biopsy (Study Day 28 or 91) should preferably be taken from the left lower lobe; the third mucosal biopsy, if done (Study Day 84 or 147) should preferably be taken from the right lower lobe.

17. Section 4.2.1 (Study Reporting Period for Adverse Events) was changed to include the following: Any new sign or symptom, disease, or other untoward medical event that occurs after the subject/legal representative signs the informed consent form, but before the subject has received the study drug, and which may possibly be causally related to the protocol (i.e., results from a required procedure or from withdrawal of prior medication), must be reported by the investigator as an adverse event in the same way as adverse events that occur after the subject receives study drug.

18. Section 4.7 (Interruption or Discontinuation of Study Dosing in Individual Subjects) was changed to include a reference to the definition of anaphylaxis in Section 4.10.

19. Section 4.10 (Monitoring of Dose Administration) was revised to include the definition of anaphylaxis. A reference was added to support the definition.

20. Section 5.5 (Secondary Endpoints) was updated to remove the PD endpoints and clarify the analyses that will be conducted.

[redacted]

Protocol Version 4.0, [redacted]

All text revisions resulting from this amendment are incorporated in the body of Protocol Version 4.0. Major changes to the protocol are described below.

1. Section 3.1.1, inclusion criterion #3 was modified for clarification.
    - If a subject has post-bronchodilator reversibility of airflow obstruction <12%, proof of ≥12% reversibility will be accepted if within 1 year of randomization.
    - Proof of a prior methacholine challenge will be acceptable for inclusion if within 1 year of randomization
    - Pulmonary was added to the exclusion of an alternative diagnosis
2. Section 3.1.1, inclusion criterion #5 was changed to remove FEV_1/ forced vital capacity (FVC) ≤ 75%.
3. Section 3.1.1, exclusion criterion #3 was changed to add eosinophilic pneumonia.
4. Section 3.1.1, exclusion criterion #4 and Section 3.3.5 were changed to allow up to 10 mg/day of oral corticosteroids if stable for at least 4 weeks prior to study drug administration.
5. Section 3.1.1, exclusion criterion #7 and Section 3.3.5 were changed to add IVIG or monoclonal therapy (eg, Xolair®) as exclusions and restricted medications.
6. Section 3.1.1, exclusion criterion #11 was changed to allow a history of cancer if more than 10 years ago.
7. Section 3.2.2, the blinding section was updated to reflect that eosinophil and basophil counts in peripheral blood will not be communicated to the site.
8. Section 3.3.4, instructions were added to add normal saline to the infusion bag in order to flush all the study drug through the IV tubing.
9. Section 3.4, a 1 day window was added to the screening bronchoscopy (7 days ± 1 day after the sputum induction).
10. Section 3.5.4, instructions for the Mantoux (PPD) test were clarified.
11. Section 3.5.5, information about the RNA and DNA tests were moved from the statistical section of the protocol (Section 5.6) to the laboratory section of the protocol.
12. Section 3.5.11.1, added long-acting β2-agonists (hold for at least 12 hours) and leukotriene modifiers (hold for at least 24 hours) to the list of medications that need to withheld prior to spirometry testing.

[redacted]

13. Section 3.5.11.3, clarified the instructions for the bronchoscopies.

14. Section 3.5.11.4, clarified the instructions for sputum induction.

15. Section 3.5.11.5, clarified the instructions for bone marrow procedures.

[redacted]

Protocol Version 5.0, [redacted]

All text revisions resulting from this amendment are incorporated in the body of Protocol Version 5.0. Major changes to the protocol are described below.

1. The Study Abstract was updated to be consistent with the changes in the body of the protocol.

2. Section 1.3 and 1.4 (Nonclinical and Clinical Experience with MEDI-563) were revised to include current information.

3. All references to single-dose or multiple-dose were removed. Subjects are randomized to Cohort 1 and Cohort 2 only.

4. All references to Study Day 91 airway biopsies and Study Day 147 End of Study/Study Termination visit were removed. The End of Study Visit for subjects in Cohort 1 is Study Day 84 and Cohort 2 will be Study Day 140. In addition Study Day 0 biopsies were renamed baseline biopsies to be more accurate. The baseline biopsy is done within 2 days prior to Study Day 0. These changes were made throughout the protocol.

5. References to legal representatives were removed from the protocol. No subjects will be enrolled who require a legal representative. It is not the intent of MedImmune to enroll a vulnerable population.

6. Section 1.5 (Rationale for Study) was updated to include the rational for Cohort 2 as follows:

   A total of 13 subjects received a single IV dose of MEDI-563 (1.0 mg/kg) or placebo (Cohort 1) in this study under previous versions of the study protocol. Cohort 1 completed the study, and the data remain blinded per protocol.

   This protocol is being amended to include the evaluation of multiple-dose SC administration (100 mg and 200 mg) instead of single or multiple-dose IV administration of MEDI-563 for the following reasons: 1) due to the potential to unblind study personnel if the study proceeds according the decision points outlined above; 2) due to the development of the SC formulation of MEDI-563; and 3) due to the intent to proceed with multiple-dose SC administration in the future. The primary objectives will remain the same.

   For this amendment, a second group of 12 subjects (Cohort 2) will be randomized in a 1:1:1 ratio to receive 1 of 2 doses of MEDI-563 (100 mg or 200 mg) or placebo as an SC injection once every 4 weeks. This cohort may be expanded by up to 3 additional subjects (for a maximum of 15 subjects) if eligible subjects are already in screening at the time 12 subjects have been randomized into the dose cohort.

7. Section 2.3 (Exploratory Objectives): Objective 2 was changed to remove end of study biopsies and mRNA expression. Inflammatory cells and proteins will be

examined in all mucosal biopsies and option biopsies obtained in Cohort 1 subjects will be examined for eosinophils.

8. Section 2.4.1 (Study Design) was updated to include the change in design. The following text was added:

   A total of 13 subjects received a single IV dose of MEDI-563 (1.0 mg/kg) or placebo (Cohort 1) in this study under previous versions of the study protocol. Cohort 1 completed the study, and the data remain blinded per protocol.

   This protocol is being amended to include the evaluation of multiple-dose SC administration (100 mg and 200 mg) instead of single or multiple-dose IV administration of MEDI-563 for the following reasons: 1) due to the potential to unblind study personnel if the study proceeds according the decision points outlined above; [redacted]; and 3) due to the intent to proceed with multiple-dose SC administration in the future. The primary objectives will remain the same.

   For this amendment, a second group of 12 subjects (Cohort 2) will be randomized in a 1:1:1 ratio to receive 1 of 2 doses of MEDI-563 (100 mg or 200 mg) or placebo as an SC injection once every 4 weeks. This cohort may be expanded by up to 3 additional subjects (for a maximum of 15 subjects) if eligible subjects are already in screening at the time 12 subjects have been randomized into the dose cohort.

9. Figure 1 was updated to be consistent with the study design and Figure 2 was removed.

10. Section 2.4.1.1 (Single-dose Administration) and 2.4.1.2 (Multiple-dose Administration) were removed because these sections were not needed as part of the study design.

11. Section 3.1.1 (Inclusion Criteria)

    a. Inclusion Criterion #3 was changed as follows in response to Health Canada:

       Previously documented diagnosis of asthma of ≥ 1 year duration, based on episodic symptoms of airflow obstruction; post-bronchodilator reversibility of airflow obstruction ≥ 12% (**in USA only -** if subject does not achieve this during screening, proof of ≥12% reversibility within 1 year of randomization is acceptable) or proof of a ~~**prior**~~ positive response to a methacholine challenge **during screening with prior approval from MedImmune (in USA only -** within 1 year of randomization **is acceptable)** as represented by a provoking concentration of methacholine to cause a 20% fall in FEV_1 (PC_{20}) < 8 mg/ml [American Thoracic Society (ATS), 2000)]; and exclusion of alternative pulmonary diagnoses (eg, cystic fibrosis, COPD);

[redacted]

b. Inclusion Criterion #5 was changed as follows in response to Health Canada. The age adjusted FEV_1/FVC ratio is the most appropriate for this population. The NHLBI guidelines will be used as a standard.

Pre-bronchodilator FEV_1/forced vital capacity (FVC) ratio that is below the age-adjusted normal limit as defined by the 2007 National Heart Lung and Blood Institute Asthma guidelines (Appendix D) and post-bronchodilator $FEV_1 \geq 65\%$ at screening;

12. Section 3.1.2 (Exclusion Criteria): Exclusion criteria were changed as follows:

a. Exclusion Criterion #4 was changed as follows to allow a similar but alternative oral corticosteroid regimen:

Current use of any systemic or inhaled immunosuppressive drugs [oral (up to a maximum dose of 10 mg/day **or 20 mg every other day**)]

b. Exclusion Criterion #11 was changed back to Protocol Version 3.0 wording in response to Health Canada

History of cancer ~~**in the past 10 years**~~, apart from basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy > 1 year prior to Study Day 0;

13. Section 3.2.1 (Subject Randomization and Treatment Allocation) was updated to reflect the current design. In addition, the following language regarding replacement of subjects was added:

Subjects who do not receive investigational product (MEDI-563 or placebo) or who do not have airway mucosal biopsy results at screening and Study Day 28 for Cohort 1 or at screening and Study Day 84 for Cohort 2 may be replaced. Additionally, subjects who receive a burst of oral corticosteroids within 28 days prior to the second airway biopsy (Study Day 28 in Cohort 1 or Study Day 84 in Cohort 2) will be replaced. The replacement subject will receive the same treatment assignment as the corresponding subject being replaced.

14. Section 3.2.2 (Blinding) was changed to remove drug supply management from those who are blinded. This group will be unblinded so they can manage the study drug packaging and inventory. In addition, a reference to the IVRS manual for study unblinding procedures was added.

15. Section 3.3 (Study Drug) was changed to remove all references to multiple doses of MEDI-563; [redacted]; [redacted] and to add Cohort 2 administration information.

16. Section 3.3.5 (Restricted Medications): 20 mg every other day was added to allowable option for oral corticosteroids.

[redacted]

17. Section 3.4 (Table 4): The following were added for clarification:

    - Asthma history. This was done as part of medical history in Cohort 1, but not discussed in the protocol.

    - Long-term follow-up for eosinophils. This was part of the protocol, but not on the study schedule.

18. Section 3.4 (Table 5): The table was changed to reflect the design change for Cohort 2. Asthma history, injection site assessments, whole blood for WBC counts (flow cytometry) and long-term follow-up were added.

19. Section 3.4.1 (Study Procedures): All references to single-dose or multiple-dose cohorts were removed; multiple-dose was changed to Cohort 2 and revised accordingly; and long-term follow-up information was added with more specific information. The study schedule was also revised to remove inconsistencies.

20. Section 3.5 (Subject Evaluation Methods): All subsections were clarified, inconsistencies were resolved, and changes were made to accommodate the change in study design.

21. Section 3.5.1 (Medical History): Asthma history was added. This was done for Cohort 1 as part of the medical history. Cohort 2 subjects will complete a specific asthma history questionnaire.

22. Section 3.5.5 (Laboratory Evaluations): The section was revised according to changes in the study schedule. In addition, clarifications were made.

23. Section 3.5.8 (Vital Signs): The section was updated to include vital sign requirements during SC dosing.

24. Section 3.5.12.1 (Office Spirometry), 3.5.12.3 (Bronchoscopy with Airway Mucosal Biopsies), and 3.5.12.4 (Sputum Induction, Collection, and Analysis) were modified to clarify procedures. Spirometry done at every visit will be completed using vendor provided equipment. Spirometry that is done for the safety of subjects surrounding the bronchoscopy and sputum induction will be done using the site's equipment and standard procedures.

25. Section 3.5.12.4 (Sputum Induction, Collection, and Analysis): The section was modified to clarify procedures and provide more specific instructions.

26. Section 3.5.12.10 (Home Peak Flow Monitoring) was modified to include more specific instructions.

27. Section 4.2.2 (Study Reporting Period for Serious Adverse Events) was modified to include the reporting period extension for subjects who qualify for long-term follow-up of peripheral blood eosinophil counts.

[redacted]

28. Section 4.5 (Other Events Requiring Immediate Reporting): Infusion reaction (Cohort 1) and anaphylactic reaction were added as immediately reportable events. This change was made to be consistent with other MedImmune protocols.

29. Section 4.6 (Safety Management During the Study): The section was clarified.

30. Section 4.9 (Dose Escalation and Dose Reduction section) was removed. There will not be multiple dose cohorts in this study and Cohort 2 is explained in the study design.

31. Section 5 (Statistical Considerations) was changed to reflect the change in study design. References to multiple dose cohorts were removed and information about Cohort 2 was put it. The sample size was changed to account for the 2 cohort design (Cohort 1 and Cohort 2).

32. Section 5.6 (Exploratory Endpoints) was changed to remove FEV_6. Only FEV_1 and FVC are being used for spirometry evaluations.

33. Appendix D was added. The Age-adjusted Lower Limit of Normal for FEV_1 and FVC Ratios (2007 NHBLI Asthma Guidelines) was added for clarification of Inclusion Criterion # 5.

Protocol Version 6.0, [redacted]

The protocol was amended to clarify changes made in Version 5.0, add additional restrictions to medications, and to correct errors.

1. Wherever "CBC with differential and platelet count" was mentioned, "platelet count" was removed. The CBC with differential includes the platelet count.
2. Section 1.5 (Rationale for Study) and Section 2.4.1 (Study Design) were updated for clarification; the long-term follow-up requirement was revised to be consistent with another MEDI-563 study (If, at the End of Study/Study Termination visit (Study Day 84 for Cohort 1 or Study Day 140 for Cohort 2), a subject's eosinophil count in peripheral blood ~~**is not at least 100 eosinohils/mm3 OR the peripheral blood eosinophil count has not returned to at least 70%**~~ **has not returned to 20% of the baseline value**, the subject will return for follow-up every other month until the subject's eosinophil count ~~**meets one of the criteria above**~~ has returned **to at least 20% of the baseline value for a maximum of one year** after the End of Study/Study Termination visit. ~~**Serious adverse events will be reported during this long-term follow-up period.**~~ Only a CBC with differential will be done at the additional follow-up visits. Information regarding blinding was removed and is contained in Section 3.3 (Blinding)
3. Section 3.1.1 (Inclusion Criteria) was updated to include: Subjects must have ≥ 2.5% eosinophils in sputum. This was mistakenly deleted in the last version of the protocol.
4. Section 3.1.2 (Exclusion Criteria) was updated to include an additional exclusion criterion: No. 18 - History of lidocaine allergy
5. Section 3.2.1 (Subject Randomization Procedures and Treatment Allocation) Cohort 2 replacement language was changed to include subjects who receive antibiotics or antivirals within 28 days prior to the second airway biopsy.
6. Section 3.2.2 (Blinding) was updated to allow for study personnel to review PK, PD, and airway biopsy results for planning future studies.
7. Section 3.3.5 (Restricted Medications) was revised to add antiviral and antibiotic medication restrictions; allow a burst of corticosteroids provided the corticosteroids are completed > 28 days prior to the Study Day 84 airway biopsy; add a restriction that influenza vaccines should not be administered to subjects within 14 days prior to the Study Day 0 or Study Day 84 bronchoscopy; and changes were made for clarification.
8. Section 3.4 (Schedule of Subject Evaluations) Table 4 - EDN, and IL-5 were added where CRP, ECP, and IL-6 are. These samples were being analyzed, but had not been listed out. The table was also updated to correlate with Section 3.4.2.
9. Section 3.4 (Schedule of Subject Evaluations) Table 5 - A sample of whole blood for WBC counts (flow cytometry) was added on Study Day 1; EDN, and IL-5 were added where CRP, ECP, and IL-6 are, serum tryptase was added on Study Day 0, Study Day 28, and Study Day 84. The table was updated to correlate with Section 3.4.2.
10. Section 3.4.1 (Study Procedures for Cohort 1) was updated to correlate with Table 4.
11. Section 3.4.2 (Study Procedures for Cohort 2) was updated to correlate with Table 5. A sample of whole blood for WBC counts (flow cytometry) was added on Study Day 1. On Study Day 28 and Study Day 56 samples for MEDI-563 concentration will only be collected

[redacted]

one time prior to administration of the investigational product. Screening bronchoscopy must be at least 7 days after the sputum induction, not 7 days ± 1 day.

12. Section 3.5.5 (Laboratory Evaluations) was updated to include EDN, IL-5, and serum tryptase. Additional information regarding the whole blood for flow cytometry was added.
13. Section 3.5.8 (Vital Signs) - A 5-minute window was added for vital signs after study drug administration. This change was made throughout the protocol as appropriate.
14. Section 3.5.9 (Pharmacokinetic Evaluations) was revised for clarification.
15. Section 3.5.12.3 (Bronchoscopy with Airway Mucosal Biopsies) was clarified. Screening bronchoscopies must be done 7 days after the sputum induction, not 7 days ± 1 day.
16. Section 5.2 (Interim Analysis) was updated to allow for study personnel to review PK, PD, and airway biopsy results for planning future studies.
17. Section 5.4 (Subject Populations) was changed to account for the replacement criteria in the protocol.
18. Section 5.5 (Primary Endpoints) was revised to include the additional lab samples (EDN, IL-5, serum tryptase, and NK cells).

[redacted]

Protocol Version 7.0, [redacted]

This protocol was amended in response to Health Canada.

1. All references to criteria for long-term follow-up were changed from "has not returned to 20% of the baseline value" back to "is not at least 100 eosinophils/mm^3 OR the peripheral blood eosinophil count has not returned to at least 70% of the baseline value, the subject will return for follow-up every other month until the eosinophil count meets one of the above criteria." In addition, assessment of SAEs was added back in during the long-term follow-up visits. This change was made to the following sections:

   - The Synopsis
   - Section 1.5 (Rationale for Study)
   - Section 3.4 (Schedule of Study Evaluations)
   - Section 3.6 (Completion of Study and Loss to Follow-up)
   - Section 4.2.2 (Study Reporting Period for Serious Adverse Events)

2. Section 3.5.12.4 (Sputum Induction, Collection, and Analysis) beginning of the fourth paragraph was changed from "If the FEV_1 is ~~>~~ (more than) 60%, the subject will inhale 3%, 4%, and 5% saline for 7 minutes each." to "If the FEV_1 is $\geq$ (more than or equal to) 60%, the subject will inhale 3%, 4%, and 5% saline for 7 minutes each."

3. Appendix E (Changes to the Protocol) Protocol Version 6.0, [redacted] was changed to include specific information about the change in follow-up that was made in Version 6.0.

[redacted]