A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Intravenously Administered MEDI-563, A Humanized Anti-interleukin-5 Receptor Alpha Monoclonal Antibody, on Asthma Control Following Acute Exacerbations in Adults

Investigational Product:	MEDI-563
MedImmune Protocol Number:	MI-CP186
IND Number:	IND 100,237
Manufacturer:	MedImmune [redacted] Phone: Fax: [redacted]
Sponsor:	MedImmune
Medical Monitor:	[redacted] Director, Clinical Development MedImmune Phone: [redacted] Fax [redacted]
Study Monitor:	MedImmune [redacted]
Protocol Date:	Original Protocol, [redacted] Amendment 1, [redacted] Amendment 2, [redacted] Amendment 3, [redacted] Amendment 4, [redacted]

Principal Investigator Agreement:

I, the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), 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), Financial Disclosure by Clinical Investigators (21 CFR 54), Institutional Review Boards (21 CFR 56) and the obligations of clinical investigators (21 CFR 312).

Signature_____ Date_____

Printed Name_____

List of Abbreviations

ACQ	Asthma Control Questionnaire
ADCC	Antibody-dependent cell cytotoxicity
AE	Adverse event
AHR	Airway hyperresponsiveness
ALT	Alanine transaminase
AQLQ(S)	Asthma Quality of Life Questionnaire (Standardized version)
AST	Aspartate transaminase
ATS	American Thoracic Society
ßHCG	Beta human chorionic gonadotropin (pregnancy test)
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of federal regulations
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CRPS	Clinical Research Pharmacy Service
CTM	Clinical trial material
CXR	Chest x-ray
ECG	Electrocardiogram
ECP	Eosinophilic cationic protein
ELISA	Enzyme-linked immunosorbent assay
ED	Emergency department
EDN	Eosinophil-derived neurotoxin
EMS	Emergency medical system
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
$IgG_{1\kappa}$	Immunoglobulin G_1 kappa
IL	Interleukin
IL-1	Interleukin-1
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-5Rα	Interleukin-5 receptor alpha
IL-6	Interleukin-6
IM	Immunogenicity
IND	Investigational new drug application
IRB	Institutional Review Board
IRE	Immediately reportable event
IV	Intravenous
IXRS	Interactive web/voice response system
MAb	Monoclonal antibody
MBP	Major basic protein
MEDI-563	Humanized $IgG_{1\kappa}$ monoclonal antibody derived from the murine, anti-human IL-5Rα MAb, MS705
PEF	Peak expiratory flow
PGA	Physician Global Assessment
PK	Pharmacokinetics
RAST	Radioallergosorbent test
RNA	Ribonucleic acid
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SID	Subject identification number
SMC	Safety monitoring committee
US	United States

WBC	White blood count

Table of Contents

List of Appendices

Study Abstract

Title: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Intravenously Administered MEDI-563, A Humanized Anti-interleukin-5 Receptor Alpha Monoclonal Antibody, on Asthma Control Following Acute Exacerbations in Adults

Objectives:

The primary objective of this study is to evaluate the effect of two IV dose regimens of MEDI 563 (0.3 and 1.0 mg/kg) on the proportion of subjects with asthma exacerbations (relapse or de novo) at Week 12 in adult subjects who required an urgent healthcare visit for treatment of an acute asthma exacerbation.

The secondary objectives of this study are to:

1) Assess the safety profile of MEDI-563 in this subject population;
2) Evaluate the effect of MEDI-563 on the proportion of subjects with asthma exacerbations (relapse or de novo) at Week 4;
3) Evaluate the effect of MEDI-563 on the proportion of subjects with asthma exacerbations (relapse or de novo) at Week 24;
4) Evaluate the effect of MEDI-563 on asthma control using the Asthma Control Questionnaire (ACQ);
5) Evaluate the effect of MEDI-563 on variability of airflow obstruction using FEV_1 at the study sites and peak expiratory flow (PEF) at home;
6) Evaluate the effect of MEDI-563 on the need to use concomitant controller or rescue medications;
7) Evaluate the effect of MEDI-563 on physician evaluation of subject status;
8) Evaluate the effect of MEDI-563 on health-related quality of life using the Asthma Quality of Life Questionnaire (AQLQ[S]);
9) Evaluate the effect of MEDI-563 on healthcare resource utilization and economics; and
10) Assess the Pharmacokinetics (PK) and immunogenicity (IM) of MEDI-563.

Study Design:

This is a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the effect of two IV dose regimens of MEDI-563 (0.3 and 1.0 mg/kg) on the proportion of subjects with asthma exacerbations (relapse and de novo) at Week 12 in adult subjects who required an

urgent healthcare visit for treatment of an acute asthma exacerbation. An urgent healthcare setting for the purposes of this study may be an emergency department or an outpatient clinic equipped to provide the level of care specified in this protocol. Approximately 15 to 20 sites in North America will participate in this study. At least 108 evaluable subjects will be randomized using a 2-step stratified randomization procedure. The first step (Step 1) will randomize subjects in a 1:1 ratio to Treatment Arms I or II, and the second step (Step 2) will randomize subjects in each treatment group in a 2:1 ratio to receive a single IV dose of MEDI-563 or placebo. Prior to being randomized into a treatment arm subjects will be stratified by baseline eosinophil levels in peripheral blood (>450 eosinophils/mm^3 vs. ≤ 450 eosinophils/mm^3). However, no subjects will be excluded based on screening eosinophil levels in peripheral blood.

Subjects are considered evaluable if they receive the investigational product, and are followed according to the protocol through Study Day 42. Nonevaluable subjects will be replaced and the new subject will receive the same treatment assignment as the replaced subject.

Investigational product (MEDI-563 or placebo) will be administered on Study Day 0 (within 7 days of meeting eligibility criteria). The subject's FEV_1 must be ≥ 30% predicted prior to administration of the investigational product.

The investigational product will be administered as a single IV infusion over a period of at least 30 minutes through a 0.22 μm protein-sparing/low in-line filter, which will be supplied by the sponsor. If the subject weighs ≥ 130 kg, the infusion time will be increased to at least 60 minutes. Subjects will be followed for a total of 24 weeks after administration of the investigational product.

Subject Population:

The subjects in this study will be adult male and female subjects who required an urgent healthcare visit for treatment of an acute exacerbation of asthma.

Treatment:

At least 108 evaluable subjects will be treated in this study, with 72 subjects receiving a single IV dose of MEDI-563 (0.3 or 1.0 mg/kg) and 36 subjects receiving a single IV dose of placebo. Investigational product (MEDI-563 or placebo) will be administered on Study Day 0 (within 7 days of meeting eligibility criteria).

Prior to administration of investigational product, all subjects will receive the same standard of care for acute asthma as described in the National Asthma Education and Prevention Program (NAEPP) Expert Report 3 (National Heart, Lung, and Blood Institute [NHLBI], 2007). Once enrolled, subjects will be given the following:

- Systemic prednisone (≥ 40 mg/day) for 7 days. The subject will be given enough oral prednisone (≥ 40 mg/day) to complete a 7-day course of treatment.
- Inhaled rescue albuterol for the remainder of the study (1 canister per month); and
- Subjects not currently taking an ICS will be given a prescription for fluticasone propionate, dose to be determined by the investigator or designee based upon severity of symptoms.

Subjects currently taking an ICS will be advised to continue using as prescribed.

Subject Evaluation and Follow-up:

Subjects will be in the study for up to 25 weeks from Screening through Study Day 168. After signing of informed consent, eligible subjects will be screened prior to administration of investigational product (MEDI-563 or placebo). Data from procedures completed as part of assessment and treatment of the asthma exacerbation (eg, blood collection for local laboratory, spirometry, and chest x-ray) may be used for screening evaluations. Screening evaluations include medical history, physical examination, electrocardiogram (ECG), chest x-ray, serum β human chorionic gonadotropin (ßHCG) for women (unless surgically sterile or at least 2 years post-menopausal), serum chemistry, hematology, and urinalysis. A negative serum or urine ßHCG for women (unless surgically sterile or 2 years after menopause) is required before investigational product administration.

Blood samples will be taken for immunoglobulin E (IgE), eosinophil cationic protein (ECP), IL-6, and C-reactive protein (CRP) on Day 0. In addition, samples may be analyzed for ribonucleic acid (RNA) transcripts, eosinophil-derived proteins such as major basic protein (MBP) and eosinophil-derived neurotoxin (EDN); plasma eotaxin levels; measurement of interleukins, and measurement of other biomarkers. Notations of ambulatory treatment for asthma prior to urgent healthcare setting arrival and treatments received in the hospital must also be recorded. Vital signs will be evaluated for 2 hours post-investigational product administration.

Subjects will be evaluated at the study site 1, 6, and 12 weeks post-dose (ie, Study Days 7 ± 1 day, 42 ± 2 days, and 84 ± 3 days). Evaluations include assessments of disease activity (spirometry, use of concomitant rescue medications, need to add inhaled steroids, and the

Physician's Global Assessment [PGA]); patient-reported outcomes (ACQ and AQLQ[S]); healthcare resource utilization and economics; safety assessments (adverse event [AE] and serious adverse event (SAE) evaluation, physical examination, vital signs, serum chemistry, hematology, urinalysis, and measurement of ECP, IL-6, and CRP); PK, and IM. In addition, samples may be analyzed for eosinophil-derived proteins such as major basic protein (MBP) and eosinophil-derived neurotoxin (EDN); plasma eotaxin levels; and measurement of interleukins. Not all evaluations will be done at each post-dose visit.

Subjects will also be contacted by telephone 4 and 9 weeks post-dose (ie, Study Days 28 ± 2 days and 63 ± 3 days) for evaluation of concomitant medications, AEs, SAEs, and asthma exacerbations, and 16, 20, and 24 weeks post-dose (ie, 112 ± 3 days, 140± 3 days, and 168± 3 days) for evaluation of asthma exacerbations.

Sample Size and Power Calculations:

Planned Sample Size

Sample size calculations have been performed for the primary endpoint of proportion of subjects with asthma exacerbations at Week 12 to allow for hypothesis testing. Sample size calculations are based on Fisher's exact test with alpha = 0.05 (2-sided) for testing the difference between the combined MEDI-563 treatment groups (n=72, 0.3 mg/kg and 1.0 mg/kg) and the combined placebo group (n=36). Assumptions include: (1) The proportion of placebo subjects with asthma exacerbations at Week 12 is 60% and (2) There will be ≥ 50% reduction in the proportion of subjects with asthma exacerbations at Week 12 in the combined MEDI-563 (0.3 and 1.0 mg/kg) treatment groups. The sample size may be re-estimated using the proportion of subjects with asthma exacerbations (relapsed or de novo) up to the first interim analysis to preserve the power around 80% if the proportion of subjects with asthma exacerbations is different from the assumptions listed above.

There will be no adjustment on Type 1 error rate for sample size re-estimation in this study. However, the true overall type I error rate will be greater than 0.05 if the multiplicity adjustment is taken into account in the calculation.

With 108 evaluable subjects, the statistical power to detect statistically significant differences in the proportion of subjects with asthma exacerbations at Week 12 in the combined MEDI-563 treatment groups and the placebo group will be 80% based on the above assumptions. Power calculations were performed using nQuery Advisor software program Version 6.01.

Re-estimation of Sample Size:

The sample size may be re-estimated based on the results of the first interim analysis as listed below.

- Sample size will be re-estimated if the proportion of subjects with asthma exacerbations (relapsed or de novo) at Week 12 is greater than or equal to 45% but less than 55%. Assumptions to re-estimate the sample size will be alpha = 0.05 (2-sided), current proportion of placebo subjects with asthma exacerbations, and a 50% reduction in the combined MEDI-563 groups.
- The sample size will not be re-estimated if the proportion of placebo subjects with asthma exacerbations (relapsed or de novo) through Week 12 is less than 45%.
- The study may be terminated if proportions of subjects with asthma exacerbations in the combined MEDI-563 groups at the interim analysis is approximately the same or lower than that in the placebo group.

Assessment of Endpoints:

The primary objective of this study is to evaluate the effect of two IV dose regimens of MEDI-563 (0.3 and 1.0 mg/kg) on the proportion of subjects with asthma exacerbations (relapsed or de novo) at Week 12 in adult subjects who required an urgent healthcare visit for treatment of an acute asthma exacerbation. The formula that will be used to evaluate the proportion of subjects with asthma exacerbations in the combined MEDI-563 treatment groups at Week 12 will be as follows:

- (Number of subjects with at least one asthma exacerbation in the combined MEDI-563 treatment groups [0.3 and 1.0 mg/kg] at Week 12) ÷ (Number of total evaluable subjects in the combined MEDI-563 treatment groups [0.3 and 1.0 mg/kg] at Week 12)

The Fisher's exact test will be performed for testing the differences in the proportion of subjects with asthma exacerbations at Week 12 between the combined MEDI-563 treatment groups and the placebo group at an alpha level of 0.05.

The number of asthma exacerbations at Week 12 for each MEDI-563 treatment group (0.3 and 1.0 mg/kg) versus placebo will also be reported. The Fisher's exact test may be performed for testing this endpoint.

The safety of MEDI-563 in this subject population is a secondary objective of this study. Adverse events will be summarized categorically by system organ class, preferred term, severity, and relationship to investigational product through Study Day 84. Serious adverse

events will be assessed through Study Day 84. Laboratory abnormalities, for tests such as serum CRP, ECP, and IL-6 levels will be evaluated in the MEDI-563 and placebo groups as changes from baseline.

Additional secondary endpoints include the effect of MEDI-563 on the:

- Proportion of subjects with asthma exacerbations (relapse or de novo) at Week 4. The formula used for the primary objective will also be used to explore the differences in proportion of subjects with asthma exacerbations for each treatment group (0.3 and 1.0 mg/kg) versus placebo and for the combined MEDI-563 treatment groups versus placebo at Week 4. The Fisher's exact test may be performed for testing this endpoint.
- Proportion of subjects with asthma exacerbations (relapse or de novo) at Week 24. The formula used for the primary objective will also be used to explore the differences in the proportion of subjects with asthma exacerbations for each treatment group (0.3 and 1.0 mg/kg) versus placebo and for the combined MEDI-563 treatment groups versus placebo at Week 24. The Fisher's exact test may be performed for testing this endpoint.
- Asthma control using the ACQ. Mean, mean change from baseline, and responder frequency tables will be provided. Individual subjects with score changes of -0.5 or less will be considered responders. A change of -0.5 is considered to be a minimally important difference on the ACQ.
- Variability of airflow obstruction using FEV_1 at the study sites and peak expiratory flow (FEV_1 and PEF) at home. Analysis will be primarily descriptive. Mean and mean change from baseline for office spirometry (FEV_1) will be provided. Two-sample t-tests may be used to explore changes from baselines in subject FEV_1 between the combined MEDI-563 treatment groups and the placebo group.
- Need to use concomitant controller or rescue medications. The analysis of the effect of MEDI-563 on the need to use concomitant controller or rescue medications during the 12-week period will be primarily descriptive.
- Physician Global Assessment (PGA).The PGA will be summarized categorically.
- Health-related quality of life using the AQLQ(S). Health-related quality of life will be evaluated using the AQLQ(S). The overall score and the 4 domain scores (symptoms, activity limitations, emotional function and environmental stimuli) are the means of the responses to the questions in each of the domains. The analyses will be primarily descriptive.
- Healthcare resource utilization and economics. The analysis of the effect of MEDI-563 on healthcare utilization and economics will be descriptive.
- PK and IM of MEDI-563. Individual MEDI-563 serum concentrations will be tabulated by treatment group along with descriptive statistics. Noncompartmental PK data analysis will be performed for MEDI-563 treated subjects, and descriptive

statistics of these noncompartmental parameters will be provided. Due the limited sampling schedule, if the data allows, population PK data analysis may be performed to better characterize the PK of MEDI-563. Immunogenicity results will be listed for each subject. Number and percentage of subjects who developed detectable anti-MEDI-563 antibodies will be summarized by treatment group (0.3 mg/kg, 1 mg/kg, or placebo). The impact of IM on PK will be assessed if data allows.

Interim Analyses

There will be 2 interim analyses. The first will be performed after at least 44 treated subjects have completed the Study Day 84 evaluations. The data will be used to re-estimate the sample size. The second will be performed after all treated subjects have completed the Study Day 84 evaluations. The primary endpoint analysis will be performed. Since the primary endpoint analysis for which this study is powered will be completed at the second interim analysis, it will not be repeated at the end of the study. All available primary endpoint data will be included in the interim analyses. In addition, analyses of limited secondary and exploratory endpoints (safety, asthma exacerbations, asthma control, and health related quality of life) will be included. These will be described in detail in the statistical analysis plan (SAP). Results from the interim analyses will be communicated to a limited number of MedImmune senior management independent of the clinical study team; these people will be identified in the unblinding plan before the interim analyses are performed. To ensure the blinding of each subject's treatment assignment throughout the study, the interim analyses will be performed by a limited number of MedImmune personnel (internal biostatisticians, programmers, and other personnel) not involved in the conduct of the study. MedImmune personnel associated with the conduct of the study, study site personnel, and subjects will remain blinded to the treatment assignment of individual subjects until the last subject completes the study and the database is locked.

1 Introduction

1.1 Background

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).

More than 300 million people around the world have asthma and despite the use of long-acting bronchodilators and inhaled corticosteroids, asthma exacerbations continue to be a major source of morbidity worldwide (Masoli et al, 2004). Hospitalizations, unscheduled visits to doctor offices, and visits to Emergency Departments (ED) occur when asthma is not under control. In North America, for example, approximately 40% of people with asthma required such care. In Western Europe, 1 in 4 people with asthma required an emergency room visit or unscheduled urgent care in the previous year. In the China/Taiwan/Mongolia region, one-third of people with asthma require urgent care, emergency room visits, or hospital admission for asthma (Masoli et al, 2004).

In the United States (US), there were 1.8 million ED visits for asthma in 2004 for an ED visit rate of 64 per 10,000 people (Moorman et al, 2007). Children had over 754,000 ED visits (ED visit rate of 103 per 10,000 children), with children aged 0 to 4 years having the highest rate at 168 per 10,000 children. Adults had an ED visit rate of 50 per 10,000 adults. The ED visit rate for black people was 350% higher than for white people. In the same year, there were 497,000 asthma hospitalizations (198,000 among children), and the asthma hospitalization rate for black people was 240% higher than for white people. Females had a hospitalization rate about 35% higher than males.

Fortunately, asthma is rarely fatal but patients who relapse after an asthma exacerbation are at increased risk of death from asthma. This is more evident when action plans are either not prescribed or not followed after leaving the hospital (Romagnoli et al, 2007). In 2004, 3,816 people died from asthma in the US for a death rate of 1.9 per 10,000 people (Moorman et al, 2007). The highest rate of death from asthma was among people 65 years of age or older (7.7 per 10,000 people) and black people (3.1 per 10,000 people).

Necropsy results have identified 2 distinct pathogenic inflammatory mechanisms of fatal asthma (Restrepo and Peters, 2008). A neutrophilic infiltrate is more prominent in those

dying suddenly (within 2 hours on onset of symptoms) while an eosinophilic infiltrate is more common in those dying from more protracted asthma crises. Many lines of evidence implicate eosinophils as one of the main causative cells of asthmatic airway inflammation (James et al, 2005). Peripheral blood eosinophilia is a risk factor for relapse of acute asthma (Janson and Herala, 1992). In subjects with peripheral blood eosinophilia, the risk of dying from asthma was 7.4 (confidence interval, 2.8-19.7) times greater than in those without eosinophilia (Ulrik and Frederiksen, 1995). Moreover, reductions in sputum eosinophilia with corticosteroids lead to better asthma control than the use of clinical guidelines (Green et al, 2006). Thus, controlling eosinophilia is associated with better asthma outcomes.

1.2 Description of MEDI-563

MEDI-563 is a humanized monoclonal antibody (MAb) that binds to the alpha chain of the interleukin-5 receptor alpha (IL-5Rα), which is shared among eosinophils and basophils. The MAb was humanized by replacing mouse for human constant regions of the IgG1κ 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 antibody-dependent cell cytotoxicity (ADCC) activity of MEDI-563.

1.3 Nonclinical Experience with MEDI-563

Nonclinical pharmacology studies showed that MEDI-563 binds to eosinophils through the IL-5Rα, blocks the binding of the ligand IL-5 to the receptor, and activates effector cells for expression of ADCC activity causing depletion of eosinophils via apoptosis within 24 to 48 hours after administration. Furthermore, 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.

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 serum 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 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 temporarily observed.

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 currently being investigated in two Phase 1 studies, MI-CP158 and MI-CP166, and one Phase 2 study, MI-CP197. MI-CP158 is an open-label, dose-escalation study to evaluate the safety and tolerability of a single IV infusion in adults with mild asthma. MI-CP166 is a double-blind, placebo-controlled study to evaluate the safety, tolerability and effects of MEDI-563, on airway eosinophils in adults with asthma. MI-CP197 is a randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety and tolerability of multiple-dose SC administration of MEDI-563.

Accrual has been completed in MI-CP158. In this study, MEDI-563 was administered as a single IV infusion of 0.0003, 0.003, 0.03, 0.1, 0.3, 1.0, or 3.0 mg/kg. A total of 44 subjects received MEDI-563 in this study. Results showed that a single IV dose of MEDI-563, as low as 0.03 mg/kg, depleted eosinophils to below the level of detection for at least 8 weeks. At the 3.0 mg/kg dose, 2 of 4 subjects experienced a cluster of adverse events (AEs) following administration of MEDI-563. One subject experienced nausea, lightheadedness, fever, chills, and headache 7 hours after the infusion, and one subject experienced headache, fever, chills, flushing, and fatigue after the infusion. A third subject had a headache after the infusion but no cluster of AEs. It was found that the site did not use a filter during infusion and the infusion time was short. No additional events were seen after a filter was required for infusion and a minimum infusion rate of at least 30 minutes was required. In the high dose groups (1.0 and 3.0 mg/kg) the eosinopenia lasted up to 12 to 16 weeks and conversely, in the low dose groups (0.003 and 0.0003 mg/kg) eosinopenia lasted an average of 2 weeks and 1 to

2 days, respectively demonstrating that the effects of MEDI-563 are dose-dependent. The pharmacokinetics (PK) of MEDI-563 was linear with dose and typical for a human IgG.

Additional clinical information can be obtained from the Investigator Brochure.

1.5 Rationale for Study

The present study will evaluate 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. Given that acute asthma in some subjects may have an eosinophilic component, administration of MEDI-563 upon discharge from an urgent healthcare setting should reduce asthma exacerbations due to better asthma control. In addition, administration of a single IV infusion of MEDI-563 may improve asthma control, particularly in those subjects who are not compliant with a continuous intake of corticosteroids to avert acute exacerbations (Burney et al, 2008).

2 Study Objectives and Overview

2.1 Primary Objective

The primary objective of this study is to evaluate the effect of two IV dose regimens of MEDI 563 (0.3 and 1.0 mg/kg) on the proportion of subjects with asthma exacerbations (relapse or de novo) at Week 12 in adult subjects who required an urgent healthcare visit for treatment of an acute asthma exacerbation.

2.2 Secondary Objectives

The secondary objectives of this study are to:

1) Assess the safety profile of MEDI-563 in this subject population;
2) Evaluate the effect of MEDI-563 on the proportion of subjects with asthma exacerbations (relapse or de novo) at Week 4;
3) Evaluate the effect of MEDI-563 on the proportion of subjects with asthma exacerbations (relapse or de novo) at Week 24
4) Evaluate the effect of MEDI-563 on asthma control using the Asthma Control Questionnaire (ACQ);

5) Evaluate the effect of MEDI-563 on variability of airflow obstruction using FEV_1 at the study sites and peak expiratory flow (PEF) at home;

6) Evaluate the effect of MEDI-563 on the need to use concomitant controller or rescue medications;

7) Evaluate the effect of MEDI-563 on physician evaluation of subject status;

8) Evaluate the effect of MEDI-563 on health-related quality of life using the Asthma Quality of Life Questionnaire (AQLQ[S]);

9) Evaluate the effect of MEDI-563 on healthcare resource utilization and economics; and

10) Assess the Pharmacokinetics (PK) and immunogenicity (IM) of MEDI-563.

2.3 Overview

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the effect of two IV dose regimens of MEDI-563 (0.3 and 1.0 mg/kg) on the proportion of asthma exacerbations (relapse and de novo) at Week 12 in adult subjects who required an urgent healthcare visit for treatment of an acute asthma exacerbation. Approximately 15 to 20 sites in North America will participate in this study. At least 108 evaluable subjects will be randomized using a 2-step stratified randomization procedure. The first step (Step 1) will randomize subjects in a 1:1 ratio to Treatment Arms I or II, and the second step (Step 2) will randomize subjects in each treatment group in a 2:1 ratio to receive a single IV dose of MEDI 563 or placebo as described in Figure 2.3-1. Prior to being randomized into a treatment arm subjects will be stratified by baseline eosinophil levels in peripheral blood (>450 eosinophils/mm^3 vs. ≤ 450 eosinophils/mm^3). However, no subjects will be excluded based on screening eosinophil levels in peripheral blood.

Subjects are considered evaluable if they receive the investigational product, and are followed according to the protocol through Study Day 42. Nonevaluable subjects will be replaced and the new subject will receive the same treatment assignment as the replaced subject.

Investigational product (MEDI-563 or placebo) will be administered on Study Day 0 (within 7 days of meeting eligibility criteria). The subject's FEV_1 must be ≥ 30% predicted prior to administration of the investigational product.

Investigational product will be administered as a single IV infusion over a period of at least 30 minutes through a 0.22 μm protein-sparing/low in-line filter, which will be supplied by the sponsor. If the subject weighs ≥ 130 kg, the infusion time will be increased to at least 60 minutes. Subjects will be followed for a total of 24 weeks after administration of the investigational product.

Subject Evaluation/Follow-up

Subjects will be in the study for up to 25 weeks from screening through Study Day 168. After signing of informed consent, eligible subjects will be screened prior to administration of investigational product (MEDI-563 or placebo). Data from procedures completed as part of assessment and treatment of the asthma exacerbation (eg, blood collection for local laboratory, spirometry, and chest x-ray) may be used for screening evaluations. Screening evaluations include medical history, physical examination, electrocardiogram (ECG), chest x-ray, serum β human chorionic gonadotropin (ßHCG) for women (unless surgically sterile or at least 2 years post-menopausal), serum chemistry, hematology, and urinalysis. A negative serum or urine ßHCG for women (unless surgically sterile or 2 years after menopause) is required before investigational product administration.

Blood samples will be taken for immunoglobulin E (IgE), eosinophil cationic protein (ECP), IL-6, and C-reactive protein (CRP) on Study Day 0. In addition, samples may be analyzed for ribonucleic acid (RNA) transcripts, eosinophil-derived proteins such as major basic protein (MBP) and eosinophil-derived neurotoxin (EDN); plasma eotaxin levels; measurement of interleukins, and measurement of other biomarkers. Notations of ambulatory treatment for asthma prior to urgent healthcare setting arrival and treatments received in the hospital must also be recorded. Vital signs will be evaluated for 2 hours post-investigational product administration.

Subjects will be evaluated at the study site 1, 6, and 12 weeks post-dose (ie, Study Days 7 ± 1 day, 42 ± 2 days, and 84 ± 3 days). Evaluations include assessments of disease activity (spirometry, use of concomitant rescue medications, need to add inhaled steroids, and the Physician's Global Assessment [PGA]); patient-reported outcomes (ACQ and AQLQ[S]); healthcare resource utilization and economics; safety assessments (AE and SAE evaluation, physical examination, vital signs, serum chemistry, hematology, urinalysis, and measurement of ECP, IL-6, and CRP); PK, and IM. In addition, samples may be analyzed for eosinophil-derived proteins such as major basic protein (MBP) and eosinophil-derived neurotoxin

(EDN); plasma eotaxin levels; and measurement of interleukins. Not all evaluations will be done at each post-dose visit.

Subjects will also be contacted by telephone 4 and 9 weeks post-dose (ie, Study Days 28 ± 2 days and 63 ± 3 days) for evaluation of concomitant medications, AEs, SAEs, and asthma exacerbations, and 16, 20, and 24 weeks post-dose (ie, 112 ± 3 days, 140± 3 days, and 168± 3 days) for evaluation of asthma exacerbations.

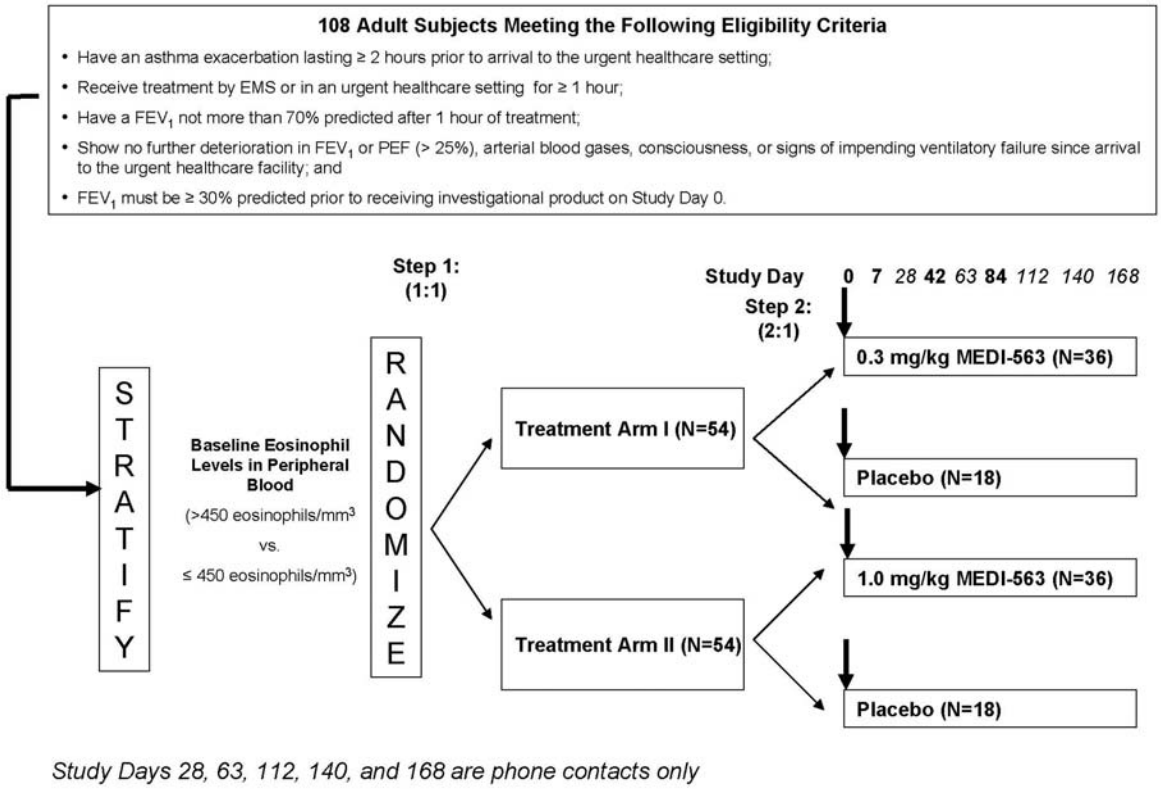


Figure 2.3-1 Study Schema

3 Study Procedures

3.1 Subject Selection

The subjects in this study will be adult male and female subjects who required an urgent healthcare visit for treatment of an acute exacerbation of asthma.

The investigator (physician) or qualified designee will discuss the study with a subject who is considered a potential candidate for the study. If there is interest in participating in the study, the subject will be provided with the informed consent form. The investigator or designee will address any questions and/or concerns that the subject may have and, if there is continued interest, will secure written informed consent for participation in the study. Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization (applies to covered entities in the US only) will be obtained prior to conducting any protocol-related procedures, including screening evaluations.

3.1.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1) Male or female subjects aged 18 to 60 years at the time of administration of investigational product.
2) Written informed consent and HIPAA authorization (applies to covered entities in the US only) obtained once the subject is considered clinically stable by the investigator, but prior to performing any protocol-related procedures. Data from procedures completed as part of the assessment and treatment of the asthma exacerbation may be used for eligibility.
3) Physician-diagnosed asthma with duration of ≥ 2 years by medical chart or subject report.
4) Had an asthma exacerbation requiring urgent care in the year prior to screening.
5) Meets NHLBI classification (Appendix 3) for persistent asthma in the 3 months prior to the current urgent healthcare visit.
6) Current asthma exacerbation that must have lasted ≥ 2 hours prior to arrival to the urgent healthcare setting.
7) Requires at least 2 treatments of inhaled bronchodilators for the current asthma exacerbation in the urgent healthcare setting or within the emergency medical system (EMS) for ≥ 1 hour.
8) Shows an FEV_1 or PEF of not more than 70% predicted after 1 hour of treatment of the current asthma exacerbation.
9) Women of child-bearing potential, unless surgically sterile (including tubal ligation) and/or at least 2 years post-menopausal, must have used 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) from screening through Study Day 84. Cessation of birth control after this point should be discussed with a responsible physician.

10) Men, unless surgically sterile, must likewise practice 2 effective methods of birth control (condom with spermicide or abstinence) and must use such precautions from Study Day 0 through Study Day 84.

11) Otherwise healthy by medical history and physical examination.

12) A chest x-ray that is normal for an asthmatic population and excludes alternative diagnosis per the investigator.

13) Ability to complete the follow-up period until Study Day 168 as required by protocol.

14) The investigator has determined that the subject is clinically stable and the $FEV_1 \geq 30\%$ predicted prior to receiving investigational product on Study Day 0,

3.1.2 Exclusion Criteria

Subjects must have *none* of the following:

1) Known history of allergy or reaction to any component of the investigational product formulation.

2) Acute illness other than asthma at the start of the study.

3) Fever > 38.6°C (>101.5°F).

4) Current acute asthma attack is due to aspirin-induced asthma.

5) Current asthma episode is an anaphylactoid/anaphylactic reaction presenting with acute bronchospasm.

6) Evidence of clinically significant non-respiratory active infection, including ongoing chronic infection.

7) History or current prolonged diarrhea, abdominal pain, and/or blood and mucus in stools or have minor symptoms AND have exposure to stream or lake water, been exposed to someone who has a parasitic infection (like a family member), or study subject has traveled to a location where parasite infestations are prevalent within the last year.

8) Use of immunosuppressive medication (except oral prednisone and inhaled and topical corticosteroids) within 30 days before randomization into the study.

9) Have received Xolair™ within 6 months before randomization into the study.

10) Receipt of immunoglobulin or blood products within 30 days before randomization into the study.

11) Receipt of any investigational drug therapy within 6 months before administration of investigational product in this study through Study Day 168.

12) History of primary immunodeficiency.

13) Previous medical history, or evidence, of an intercurrent illness that may compromise the safety of the subject in the study.

14) History of clinically significant abnormality on ECG in the opinion of the investigator.

15) Pregnancy (must have a negative serum pregnancy test prior to administration of investigational product).

16) Breastfeeding or lactating woman.

17) History of treatment for alcohol or drug abuse within the past year.

18) Diagnosis of COPD by a health care professional

19) Evidence of any clinically significant systemic disease on physical examination.

20) History of cancer except basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy > 1 year prior to entry or other malignancies treated with apparent success with curative therapy > 5 years prior to entry.

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

22) Any condition (ie, impending ventilatory failure or hemodynamic compromise) that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of study results.

23) Any employee of the clinical study site who is involved with the conduct of the study.

24) History of cigarette smoking > 20 pack years

25) Previously received MEDI-563.

26) Asthma exacerbation due to acute inhalational exposure.

3.2 Enrollment and Randomization

A subject is considered enrolled into the study once written informed consent is obtained. Once informed consent is obtained, a subject identification number (SID) will be assigned by a central system (eg, an interactive voice/web response system [IXRS]) and the screening evaluations may begin. This number will be used to identify the subject during the screening process and throughout study participation.

Enrolled subjects will be screened by investigators to assess eligibility for randomization into the study. A master log will be maintained of all enrolled subjects and will document all screening failures (ie, subjects who are consented and enrolled but not randomized), including reason for screening failure.

Subjects who fail to meet all eligibility criteria or who decline participation will not proceed to randomization.

An IXRS will be used for assignment of the SID at enrollment, randomization to a treatment arm and treatment group, and assignment of blinded investigational product kit numbers. A subject is considered entered and randomized into the study when the investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of a blinded investigational product kit number to the subject using the 2-step stratified randomization procedure described in Section 2.3 and displayed in Figure 2.3-1.

The procedure for study entry and randomization is as follows:

- The subject has been treated for asthma exacerbation in the urgent healthcare setting or in the EMS for ≥ 1 hour and meets all the inclusion and exclusion criteria.
- The investigator or designee confirms that written informed consent has been obtained and that the subject meets all eligibility criteria.
- The investigator or designee calls or logs onto the IXRS and provides the SID and subject's baseline characteristic(s) used to verify that it is the same subject, and the subject's eosinophil count.
- At the first step of randomization, the IXRS assigns a treatment arm (Treatment Arm I or II) to the subject at a 1:1 ratio. Then at the second step, IXRS assigns the subject to a treatment group at a 2:1 ratio (MEDI-563 and placebo, respectively), and assigns an investigational product kit number(s). Both steps will be done on the same call or login.
- A confirmatory fax with this information is sent to the Clinical Trial Material (CTM) Manager.

Investigational product (MEDI-563 or placebo) must be administered as soon as possible after randomization. If there is a delay in the administration of investigational product such that it will not be administered on the day of receipt of the investigational product kit number(s), the MedImmune study monitor and/or its designee must be notified immediately.

Subjects are considered evaluable if they receive the investigational product and are followed according to the protocol through Study Day 42. Nonevaluable subjects will be replaced. Replacements, if necessary will take place after the initial randomization of all planned subjects has been completed. The replacement subject will receive the same treatment assignment as the subject being replaced.

3.3 Blinding

This is a double-blind study. The CTM Manager who prepares the investigational product will be blinded to treatment (MEDI-563 or placebo), but will know the dose (0.3 mg/kg or 1.0 mg/kg). The prepared investigational product will be injected into pre-filled infusion bags identical in appearance and volume for IV administration; therefore, subjects and study personnel, including the investigators, study nurses, and coordinators, will be blinded to treatment assignment. All protocol-associated MedImmune personnel or designees, including the medical monitor, project manager, the statistician, and the site monitors, will also be blinded to treatment assignments.

The vendor for packaging and labeling of the clinical supplies, IXRS personnel, the CTM Manager, MedImmune Clinical Research Pharmacy Service (CRPS) personnel, and designated persons in MedImmune Quality Assurance are the only individuals who will have access to information that may identify a subject's treatment allocation. These individuals must not reveal randomization or treatment information to anyone or participate in or be associated with the evaluation of study subjects.

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 counts (including eosinophil-derived proteins and eotaxin) and basophil counts will not be communicated to the site personnel who evaluate the subjects clinically, except if the information is required for management of AEs. Communication between the site and the MedImmune medical monitor should happen prior to disclosure of the eosinophil and basophil counts to the site. In the event that the treatment allocation for a subject becomes known to the investigator or other study staff or needs to be known to treat an individual subject for an AE, the sponsor must be notified immediately by the investigator. For the purpose of unblinding due to any emergent safety issues, the investigator should follow the instructions for unblinding contained in the IXRS manual.

There will be 2 interim analyses. The first interim analysis will be performed after at least 44 treated subjects have completed the Study Day 84 evaluations. The second interim analysis will be performed after all treated subjects have completed the Study Day 84 evaluations. Results from the interim analyses will be communicated to a limited number of MedImmune senior management independent of the clinical study team; these people will be identified in the unblinding plan before the interim analyses are performed. To ensure the blinding of each subject's treatment assignment throughout the study, the interim analyses will be performed

by a limited number of MedImmune personnel (internal biostatisticians, programmers, and other personnel) not involved in the conduct of the study. MedImmune personnel associated with the conduct of the study, study site personnel, and subjects will remain blinded to the treatment assignment of individual subjects until the last subject completes the study and the database is locked.

3.4 Investigational Product (MEDI-563 and Placebo)

3.4.1 Investigational Product Supplies and Accountability

Investigational product will be distributed to clinical sites using designated distribution centers. The sponsor will provide the investigators with adequate quantities of investigational product. All investigational products will be stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.

Investigational product will be supplied to the CTM Manager 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 investigational product from the CTM Manager using the site's normal ordering procedures. The CTM Manager will prepare the investigational product MEDI-563 (5 mg or 50 mg/vial) and placebo. Sites in Canada will use only the 5 mg/mL formulation. Sites in the USA may use the 5 mg/mL or the 50 mg/mL formulation.

MEDI-563 (50 mg/mL): MEDI-563 is supplied in 3 mL vials filled with 1.2 mL solution of MEDI-563 at a concentration of 50 mg/mL, containing 10 mM histidine, 300 mM glycine, 0.02% polysorbate-20, pH 6.0.

Placebo: Placebo is supplied in 3 mL vials filled with 1.2 mL solution of 10 mM histidine, 300 mM glycine, 0.02% polysorbate-20, pH 6.0.

MEDI-563 (5 mg/mL): MEDI-563 is supplied in 10 mL vials filled with 9.5 mL solution of MEDI-563 at a concentration of 5 mg/mL, containing 10 mM sodium citrate buffer, 150 mM sodium chloride, 0.02% polysorbate-80, pH 6.0.

Placebo: Placebo is supplied in 10 mL vials filled with 9.5 mL solution of 10 mM sodium citrate buffer, 150 mM sodium chloride, 0.02% polysorbate-80, pH 6.0.

Specific details regarding investigational product supplies, dose preparation, and accountability will be provided in the CTM Manual supplied to the sites.

The CTM Manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of all investigational product accountability records will be returned to the sponsor. All unused investigational product will be returned to MedImmune or disposed of upon authorization by MedImmune (refer to the CTM Manual for contact information and specific shipping instructions).

3.4.2 Treatment Regimen

At least 108 evaluable subjects will be treated in this study, with 72 subjects receiving a single IV dose of MEDI-563 (0.3 or 1.0 mg/kg) and 36 subjects receiving a single IV dose of placebo as described in Table 3.4.2-1. Investigational product (MEDI-563 or placebo) will be administered on Study Day 0 (within 7 days of meeting eligibility criteria) once the subject has demonstrated an FEV_1 of ≥ 30% predicted.

Table 3.4.2-1 Summary of Treatment Regimens

Treatment Arm	Number of Subjects	Treatment Regimen
1	36	0.3 mg/kg IV MEDI-563 on Study Day 0
	18	Placebo on Study Day 0
2	36	1.0 mg/kg IV MEDI-563 on Study Day 0
	18	Placebo on Study Day 0

Prior to administration of investigational product, all subjects will receive the same standard of care for acute asthma as described in the National Asthma Education and Prevention Program (NAEPP) Expert Report 3 (National Heart, Lung, and Blood Institute [NHLBI], 2007). Once enrolled, subjects will be given the following:

- Systemic prednisone (≥ 40 mg/day) for 7 days. The subject will be given enough oral prednisone (≥ 40 mg/day) to complete a 7-day course of treatment.
- Inhaled rescue albuterol for the remainder of the study (1 canister per month); and

- Subjects not currently taking an ICS will be given a prescription for fluticasone propionate, dose to be determined by the investigator or designee based upon severity of symptoms.

Subjects currently taking an ICS will be advised to continue using as prescribed.

3.4.3 Investigational Product Preparation

The dose of investigational product for administration must be prepared by the CTM Manager using aseptic technique. Detailed instructions regarding investigational product preparation can be found in the CTM Manual that will be provided to the CTM Manager.

The dose of investigational product will be calculated by the CTM Manager based on the subject's weight on the dosing day.

The dose will be calculated using the following formula:

$$\frac{\text{Dose (mL)} = \text{Weight (kg)} \times \text{Dose (mg/kg)}}{\text{5 mg/mL or 50 mg/mL}}$$

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 mL for the 5 mg/mL formulation or 1.6 mL for the 50 mg/mL formulation.

3.4.4 Administration of Investigational Product

The investigational product 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 investigational product contains no bacteriostatic agents.

The investigational product should be dispensed by the pharmacist or qualified designee and administered as an IV infusion. All infusions must be administered over a period of at least 30 minutes using a 0.22 μm protein-sparing/low in-line filter, which will be supplied by the sponsor. If the subject weighs ≥ 130 kg, the infusion time will be increased to at least 60 minutes.

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

On Study Day 0, vital signs (blood pressure, temperature, pulse rate, and respiratory rate) will be taken prior to administering the investigational product, every 15 minutes (± 5 minutes) during investigational product administration, and immediately after investigational product administration (+ 5 minutes). Subjects will be observed at the study site for a minimum of 2 hours after the end of the infusion, during which time adverse reactions to the investigational product will be monitored. If an adverse reaction occurs, the subject will be monitored until the event resolves. Vital signs (blood pressure, temperature, pulse rate, respiratory rate) will be checked just prior to discharge. Section 4.9 provides additional information regarding monitoring dose administration.

3.4.5 Concomitant Medications

Use of concomitant medications, other than those provided per protocol (systemic prednisone [≥ 40 mg/day] for 7 days, inhaled rescue albuterol for the entire study period, and ICS as prescribed, see Section 3.4.2) from Study Day 0 through Study Day 84 are discouraged. However, subjects may receive medications to treat AEs as deemed necessary by the investigator or the subject's physician.

All concomitant medications given to the subject from screening through Study Day 84, including those given in the urgent healthcare setting or in the EMS to treat the initial acute asthma exacerbation will be recorded on the source document. The following medications are considered exclusionary, and the sponsor must be notified if a subject receives any of these through Study Day 84.

1) Immunosuppressive medication (corticosteroids are permitted)
2) Investigational agents
3) Xolair®

3.5 Schedule of Subject Evaluations

All subjects who are assigned a SID and receive any investigational product will be followed according to the protocol regardless of the number of doses received, unless consent for follow-up is withdrawn. The investigator must notify the sponsor or designee 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. Protocol deviations will be recorded on the source document with an explanation for the deviation. The investigator must

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

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

A schedule of screening and on-study visit procedures is presented in Table 3.5-1, followed by a detailed description of each visit.

Table 3.5-1 Schedule of Subject Evaluations

Study Day	Screen [a]	0 [b]	7	28	42	63	84	112	140	168
	Screening	**Visit 1**	**Visit 2**	**Phone Contact**	**Visit 3**	**Phone Contact**	**Visit 4**	**Phone Contact**	**Phone Contact**	**Phone Contact**
Written Informed Consent and HIPAA	X									
Verify Eligibility Criteria	X	X								
Medical and asthma history	X									
Chest X-ray	X									
ECG	X									
Serum ßHCG	X [c, d]									
Urine ßHCG		X [c, e]					X			
Concomitant Medications	X	X	X	X	X	X	X			
Randomization and Assignment of Study Product Kit Number		**X**								
Investigational Product Administration		**X**								
Safety Evaluations										
Physical Examination	X	X [e]	X		X		X			
Vital Signs	X	X	X		X		X			
Serum Chemistry	X [d]	X	X		X		X			
Hematology	X [d]	X	X		X		X			
Urinalysis	X [d]	X	X		X		X			

Table 3.5-1 Schedule of Subject Evaluations

Study Day	Screen [a]	0 [b]	7	28	42	63	84	112	140	168
	Screening	Visit 1	Visit 2	Phone Contact	Visit 3	Phone Contact	Visit 4	Phone Contact	Phone Contact	Phone Contact
CRP, ECP, and IL-6		X	X		X		X			
Assessment of Adverse Events	X	X	X	X	X	X	X			
Assessment of Serious Adverse Events	X	X	X	X	X	X	X			
Disease Activity										
Assessment of asthma exacerbation			X	X	X	X	X	X	X	X
Spirometry or Peak Flow	X									
Spirometry		X	X		X		X			
Serum sample for possible analysis of interleukins, eosinophil derived proteins, and eotaxin		X	X		X		X			
RNA transcripts (PAXgene™ tubes)		X					X			
Serum sample for biomarkers		X					X			
Mast cell tryptase, histamine, TNF-alpha, and IL-1		X [f]								
RAST IgE		X	X							
Physician Global Assessment					X		X			
Collect Home Peak Flow Monitoring Data and Rescue Medications			X		X		X			

Table 3.5-1 Schedule of Subject Evaluations

Study Day	Screen [a]	0 [b]	7	28	42	63	84	112	140	168
	Screening	Visit 1	Visit 2	Phone Contact	Visit 3	Phone Contact	Visit 4	Phone Contact	Phone Contact	Phone Contact
Patient Reported Outcomes										
ACQ		X	X		X		X			
AQLQ(S)		X			X		X			
PK/IM										
MEDI-563 serum Concentration		X [g]	X		X		X			
Anti-MEDI-563 Antibodies		X					X			

a Screening must occur within 7 days of investigational product administration. Any procedures completed as part of the assessment and treatment of the asthma exacerbation may be used for screening (eg, serum chemistry, hematology, urinalysis, ßHCG if applicable, spirometry, chest x-ray, ECG).

b Screening and Study Day 0 may be the same day. If more than 7 days apart, contact the medical monitor about screening evaluations that may need to be repeated.

c For women of childbearing potential, must be negative prior to investigational product administration

d Analyzed at local lab

e Only if screening and Study Day 0 are not on the same day

f Prior to dosing, and in the event of an anaphylactic or infusion reaction, after the end of the infusion

g Prior to administration of investigational product and one hour after the end of the infusion

Screening

Screening and Study Day 0 may occur on the same day. If investigational product administration is more than 7 days after screening evaluations, the medical monitor must be contacted. Written informed consent and HIPAA (applies to covered entities in the US only) must be obtained prior to performing any study-related procedure, including screening evaluations.

Any evaluations performed for other purposes (ie, as part of asthma exacerbation) prior to informed consent that are otherwise suitable for use as screening evaluations, need not be repeated.

1) Written informed consent and HIPAA once the investigator feels the subject is clinically stable
2) Assign an SID
3) Verify eligibility criteria
4) Perform medical history and asthma history
5) Perform physical examination

   Note: Items 4 and 5 above are designed to collect information on the subject once enrolled into the study and these start the screening process. Any new physical exam finding, symptom, disease, or untoward medical event that begins after written informed consent has been obtained, but before receipt of investigational product, that is not related to a protocol requirement must be added to the baseline medical history or physical exam.
6) Perform chest x-ray
7) Perform ECG
8) Urinalysis (analyzed at local laboratory)
9) Spirometry or peak flow- Note: If qualifying spirometry or peak flow (ie, for inclusion criterion number 8) has been performed prior to signing of informed consent, then the screening spirometry or peak flow need not be repeated
10) Vital signs including temperature, blood pressure, pulse rate, and respiratory rate
11) Blood collection for:
    - Serum chemistry (analyzed at local laboratory)
    - Hematology (analyzed at local laboratory)
    - Serum βHCG (For women of childbearing potential only. Must be negative prior to administration of investigational product). Will be analyzed at local

laboratory, with results known prior to administration of investigational product.

12) Assess for SAEs and protocol-related AEs

13) Record concomitant medications and medications received in urgent healthcare setting for current asthma exacerbation

Study Day 0 (Infusion)

Visit 1

1) Urine ßHCG if screening and Study Day 0 are not on the same day (for women of childbearing potential only). Must be negative prior to administration of investigational product

2) Record concomitant medications

3) Physical examination (if screening and Study Day 0 are not on the same day)

4) Verify eligibility criteria

5) Randomization and assignment of study product kit number

6) ACQ

7) AQLQ(S)

8) Spirometry

9) Urinalysis

10) Blood collection for:

- Serum chemistry (sent to central laboratory)
- Hematology (sent to central laboratory)
- CRP, ECP, IL-6
- Possible analysis of interleukins, eosinophil derived proteins, and eotaxin
- RNA transcripts
- Biomarkers
- Mast cell tryptase, histamine, TNF-alpha, and IL-1
- Radioallergosorbent test (RAST) IgE
- MEDI-563 serum concentration
- Anti-MEDI-563 antibodies

11) Vital signs before administration of investigational product

NOTE: All assessments listed above need to be completed prior study drug administration

12) Administration of investigational product

13) Monitor for AEs and SAEs

14) Record any additional concomitant medications, if applicable

15) Monitor vital signs every 15 (± 5 minutes) minutes during investigational product administration, immediately after completion of the investigational product administration (+ 5 minutes), and for a minimum of 2 hours after the end of the infusion.

16) Collect blood for additional MEDI-563 serum concentration 1 hour after the end of the infusion

17) Provide home peak flow meter and ensure subject understands how to use it; provide instructions for collection of rescue medication use

18) Provide discharge medications (systemic prednisone ≥ 40 mg/day for 7 days, and inhaled rescue albuterol for the entire study period), and either a prescription for fluticasone propionate, [dose to be determined by the investigator or designee based upon severity of symptoms (subjects not on ICS)], or instructions to continue using ICS as previously prescribed.

Study Day 7: Follow-up after Infusion (±1 day)

Visit 2

1) ACQ

2) Assessment of asthma exacerbation

3) Physical examination

4) Collect home peak flow monitoring data and use of rescue medications

5) Record concomitant medications

6) Assess for AEs and SAEs

7) Vital signs

8) Spirometry

9) Blood collection for:

- Serum chemistry
- Hematology
- CRP, ECP, IL-6
- Possible analysis of interleukins, eosinophil derived proteins, and eotaxin
- RAST IgE
- MEDI-563 serum concentration

10) Urinalysis

Study Day 28: Follow-up Phone Call (± 2 days)

1) Record concomitant medications
2) Assess for AEs and SAEs
3) Assess for asthma exacerbation

Study Day 42: Follow-up after Infusion (± 2 days)

Visit 3

1) ACQ
2) AQLQ(S)
3) Assessment of asthma exacerbation
4) Physical examination
5) Physician global assessment
6) Collect home peak flow monitoring data and use of rescue medications
7) Record concomitant medications
8) Assess for AEs and SAEs
9) Vital signs
10) Spirometry
11) Blood collection for:
    - Serum chemistry
    - Hematology
    - CRP, ECP, IL-6
    - Possible analysis of interleukins, eosinophil derived proteins, and eotaxin
    - MEDI-563 serum concentration
12) Urinalysis

Study Day 63: Follow-up Phone Call (± 3 days)

1) Record concomitant medications
2) Assess for AEs and SAEs
3) Assess for asthma exacerbation

Study Day 84: Last Study Visit (± 3 days)

Visit 4

1) ACQ
2) AQLQ(S)
3) Assessment of asthma exacerbation
4) Physical examination
5) Physician global assessment
6) Collect home peak flow meter, home peak flow monitoring data, and use of rescue medications
7) Record concomitant medications
8) Assess for AEs and SAEs
9) Vital signs
10) Spirometry
11) Blood collection for:
    - Serum chemistry
    - Hematology
    - CRP, ECP, IL-6
    - Possible analysis of interleukins, eosinophil derived proteins, and eotaxin
    - RNA transcripts
    - Biomarkers
    - MEDI-563 serum concentration
    - Anti-MEDI-563 antibodies
12) Urinalysis
13) Urine ßHCG

Study Day 112: Follow-up Phone Call (± 3 days)

1) Assess for asthma exacerbation

Study Day 140: Follow-up Phone Call (± 3 days)

1) Assess for asthma exacerbation

Study Day 168: Follow-up Phone Call (± 3 days)

1) Assess for asthma exacerbation

3.6 Subject Evaluation Methods

3.6.1 Medical History and Asthma History

Medical history by body system will be completed during screening. Any new physical exam finding, symptom, disease, or untoward medical event that begins after written informed consent has been obtained, but before receipt of investigational product, that is not related to a protocol requirement must be added to the medical history or physical exam.

The asthma history questionnaire, also completed as part of the screening evaluations, includes questions related to the subject's asthma history, asthma medications, asthma-related urgent healthcare visits, and asthma-related hospitalizations.

3.6.2 Chest X-ray

All subjects will have a chest x-ray during screening. The chest x-ray cannot reveal a diagnosis other than asthma that in the opinion of the investigator provides an explanation for the subject's symptoms

3.6.3 ECG

A 12-lead ECG will be done during screening. If abnormal, the investigator must qualify the ECG abnormality as clinically significant or not clinically significant. If the ECG is abnormal, clinically significant the subject may not enroll in the study.

3.6.4 Physical Examination

Physical examinations will be performed at intervals designated on the study schedule (Table 3.5-1). The examination will include assessments by body system, height (screening only), and weight.

Any new physical exam finding, symptom, disease, or untoward medical event that begins after written informed consent has been obtained, but before receipt of investigational

product, that is not related to a protocol requirement must be added to the baseline medical history or physical exam.

Medically significant changes from the screening physical examination will be considered AEs and recorded as such on the validated data collection instrument provided (ie, a paper case report form or electronic data screen).

3.6.5 Laboratory Evaluations

Screening laboratory evaluations that are necessary for inclusion in the study (ie, serum chemistry, hematology, urinalysis, and serum ßHCG if applicable) will be analyzed at a licensed local laboratory. All other laboratory samples will be analyzed by a central laboratory.

If screening and Study Day 0 occur on the same day, samples will be sent to the local laboratory (screening) and the central clinical laboratory (Study Day 0).

Urine pregnancy tests during the study will be performed in the clinic using a licensed test. Medically significant abnormal laboratory results should be repeated as soon as possible (preferably within 24-48 hours).

Investigators must review results from the local laboratory for serum chemistry, hematology, urinalysis, and serum and urine ßHCG prior to giving the subject investigational product on Study Day 0.

After the screening values are obtained, study site personnel must not be aware of the peripheral blood eosinophil and basophil counts of study subjects, except if required to manage AEs upon discussion with the MedImmune medical monitor.

3.6.5.1 Routine Laboratory Evaluations

A laboratory manual will be provided specifying procedures for collection, processing, storage, and shipping of samples. Routine laboratory assessments include the following:

- Hematology: includes complete blood count (CBC) with differential (including eosinophils), platelets, and hemoglobin.
- Serum chemistry: includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, creatinine phosphokinase (CPK), aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, alkaline phosphatase, random glucose,

and troponin. A fractionated CPK will be completed for any samples that yield an elevated CPK value.

- Urinalysis: includes urine dipstick tests.

3.6.5.2 Pregnancy Tests

Pregnancy test results will need to be reviewed by the investigator or designee prior to administration of investigational product. The following test will be used to monitor pregnancy in women of child-bearing potential:

- Serum ßHCG during screening only, for women of childbearing potential, unless surgically sterile or at least 2 years post-menopausal.
- Urine pregnancy tests will be performed using a licensed test at visits designated on the study schedule, for women of childbearing potential, unless surgically sterile or at least 2 years post-menopausal.

3.6.5.3 Other Laboratory Evaluations

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

- RAST IgE antibody test
- Serum CRP, ECP, and IL-6
- Serum samples for possible analysis of interleukins, eosinophil derived proteins, and eotaxin
- RNA (PAXgene™ tubes)_
- Serum sample for biomarkers
- Serum sample for mast cell tryptase, histamine, TNF-alpha, and IL-1.
- Additional serum sample for histamine, mast cell tryptase, TNF-alpha, and IL-1 will be obtained from any subject suspected to have an anaphylactic reaction or infusion reaction.

3.6.6 Pharmacokinetic Evaluations

Blood samples (to be processed in serum) for MEDI-563 concentration determination will be collected at all study visits. When the investigational product is administered, a sample will be collected immediately before investigational product administration and 1 hour after the end of the infusion. Instructions for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to the sites.

3.6.7 Immunologic Evaluations

The presence of anti-MEDI-563 antibodies will be evaluated in serum. The study schedule outlines when these samples will be collected. Instructions for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to the sites.

3.6.8 Vital Signs

Vital signs, including temperature, blood pressure, pulse rate, and respiratory rate will be obtained at every visit. When investigational product is administered, vital signs will be obtained prior to the infusion, every 15 minutes (± 5 minutes) during infusion, immediately after infusion (+ 5 minutes), and just prior to discharge from the study site, which will be at least 2 hours after the end of the infusion.

3.6.9 Concomitant Medications

Study subjects will be given systemic prednisone (≥ 40 mg/day for 7 days) and inhaled rescue albuterol for the duration of the study (1 canister per month). In addition, subjects not currently taking an ICS will be given a prescription for fluticasone propionate, dose to be determined by the investigator or designee based upon severity of symptoms. Subjects currently taking an ICS will be advised to continue using as prescribed. Subjects will be instructed on medication use and these will be recorded on the source document and in the validated data collection instrument provided.

Use of concomitant controller and rescue medication will be collected daily by the subject from screening through Study Day 84. Instructions will be provided to each enrolled subject at screening/Study Day 0. At each follow up visit, subjects will be assessed specifically for the need to add ICS and this will be recorded.

All other concomitant medications the subject takes, including vitamins and supplements from screening through study termination will be recorded.

3.6.10 Disease Evaluations

3.6.10.1 Asthma Exacerbations

Asthma exacerbation data will be collected through Study Day 168. For the purpose of this study, an asthma exacerbation (relapse or de novo) is defined as either 1) an increase of asthma symptoms (cough, wheeze, chest tightness, and/or shortness of breath) that does not resolve within 2 hours after the use of rescue albuterol or corticosteroids and requires an unscheduled medical visit or 2) during a scheduled study visit, the subject has acute worsening of asthma symptoms and a reduction of ≥ 20% in PEF or FEV_1, which in the opinion of the investigator requires treatment with systemic corticosteroids.

An exacerbation event will be considered resolved if the subject's acute asthma symptoms diminish or PEF or FEV_1 return to > 80% of baseline for > 7 days after completion of oral steroid burst therapy.

The following information will be collected for each asthma exacerbation:

- Date of onset
- Date of visit to healthcare provider or ED
- Treatment
- Resolution date

In this study, 2 aspects of asthma exacerbations will be collected: (1) number of subjects with at least one exacerbation during the study, and (2) number of exacerbations per subject in each treatment group.

3.6.10.2 Office Spirometry

Pulmonary function will be assessed via measurement of airflow limitation according to the study schedule.

Spirometry will be performed at study sites by the investigator or qualified designee according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Miller et al, 2005) at every visit. Spirometry should be performed with the subject in the sitting position. Multiple forced expiratory efforts (at least 2 but no more than 5) 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 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. Equipment, training, and a procedures manual will be provided to the site by a qualified vendor.

3.6.10.3 Home Peak Flow Testing

Home peak flow testing for FEV_1 and PEF will be performed daily from screening through Study Day 84. Subjects are to be at least 80% compliant with home peak flow testing. Compliance of < 80% is considered a protocol deviation.

Subjects should perform peak flow testing every morning while sitting or standing prior to using albuterol (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. Peak flow meters for home and instructions for data recording will be provided to each enrolled subject at screening/Study Day 0.

3.6.10.4 Physician Global Assessment

The Physician Global Assessment will be completed according to the study schedule. It consists of a single physician rated question of subject status.

3.6.11 Patient Reported Outcomes

3.6.11.1 Asthma Control Questionnaire

The ACQ (see sample in Appendix 4) will be completed at visits specified in the study schedule. The ACQ is a 6-item subject reported questionnaire to assess the recall over the prior week with 6 items addressing night-time waking, symptoms on waking, activity limitation, shortness of breath, wheeze, and rescue short-acting beta agonist use (Juniper et al, Oct 1999). Questions are rated on a 7-point Likert scale from 0 (no impairment) to 6 (maximum impairment) where scores of ≤ 0.75 indicate well-controlled asthma and scores >1.5 indicate uncontrolled asthma (Juniper et al; 2006). Individual changes of 0.5 are considered to be clinically meaningful (Juniper et al, 2005)

Although not required by protocol, it is preferable if the ACQ is the first assessment completed during the study visit.

3.6.11.2 Asthma Quality of Life Questionnaire (Standardized Version)

The AQLQ(S) (see sample in Appendix 5), will be completed at visits specified in the study schedule. The AQLQ(S) is a 32-item questionnaire that measures the functional impairments experienced by adults 17 years and older (Juniper et al, May 1999). It has 4 domains (symptoms, activity limitations, emotional function, and environmental stimuli). Subjects are asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale from 7 = no impairment to 1 = severe impairment. The overall score is calculated as the mean response to all questions. The 4 domain scores (symptoms, activity limitations, emotional function and environmental stimuli) are the means of the responses to the questions in each of the domains. Individual improvement for both the overall and individual domain scores of 0.5 have been identified as the minimally important difference, with changes >1.5 to be large meaningful differences (Juniper et al, 1994).

Although not required by protocol, it is preferable if the AQLQ(S) is completed after the ACQ and prior to other assessments.

3.6.11.3 Healthcare Resource Utilization and Economics

Healthcare resource use will be summarized from information on asthma exacerbations, and asthma related medications. Absolute number and proportion of healthcare resource utilization by resource type will be reported.

3.7 Completion of Study and Loss to Follow-up

Subjects will be considered to have completed the study if they were followed up through Study Day 168. It should be specified on the source document whether or not the subject completed the study follow-up procedures through Study Day 168.

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 168. Investigators 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.

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 dosage higher than that prescribed by a healthcare professional for clinical reasons, or a dosage 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 nonclinical reasons) of an investigational or marketed product;
- An event related to a medical procedure or associated with the discontinuation of the previous use of an investigational or marketed product required by protocol (protocol-related AE).

4.1.2 Study Reporting Period for Adverse Events

All adverse events that occur after a subject has received the investigational product through Study Day 84 must be reported by the investigator.

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 investigational product, and which may possibly be causally related to the protocol (ie, 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 investigational product.

4.1.3 Recording of Adverse Events

All AEs will be recorded using the collection instrument 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 investigational 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 immediately life-threatening

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

  A pregnancy should be reported to MedImmune Product Safety as an immediately reportable event (IRE). A pregnancy should be followed for outcome and the health status of the mother and the child. If the child is born with any congenital anomaly of birth defect, this should be reported to Product Safety as a SAE.

- 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 an SAE (protocol-related SAE).

4.2.2 Study Reporting Period for Serious Adverse Events

The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through Study Day 84. 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 an 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 an SAE that is suspected by the investigator or qualified designee to be related to investigational 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 an SAE, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must complete the SAE Report form and fax to MedImmune Product Safety.

MedImmune contact information:

Product Safety
MedImmune
[redacted]
Fax: [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 SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by 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 an 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 SAEs 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 through Study Day 84. 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 investigational 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.

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 1).

Another consideration to assist investigators in distinguishing between severity levels would include the level of medical intervention required in response to the adverse event. 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 general symptomatic medical intervention by a health care professional. In contrast, a *Severe* adverse event would generally require more immediate medical evaluation and intervention by a health care professional.

Mild: Mild level of discomfort and does not interfere with regular activities
Moderate: Moderate level of discomfort and significantly interferes with regular activities
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 an 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 an 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 investigational product. 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 SAEs to the investigational product. A number of factors should be considered in making this assessment including: 1) the temporal relationship of the event to the administration of investigational 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 investigational product administration.

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

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

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

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

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

For AEs that occur prior to the administration of investigational product, an assessment of protocol relatedness must be made. Protocol-related AEs may occur as a result of procedures required during the screening process (eg, blood collection, washout of an existing medication) prior to the initial administration of investigational product. For AEs that occur before administration of investigational product, only those that are assessed by the investigator as protocol-related should be reported to the sponsor. The following guidelines should be used by investigators to assess the relationship of an AE to a protocol-required procedure:

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

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

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) Anaphylactic (see Section 4.7) or infusion reaction (see Section 4.9)

* Subjects who become pregnant from Study Day 0 through Study Day 84 will be followed for the duration of the 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.

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 through Study Day 84. The MedImmune Product Safety Specialist has responsibility for the day-to-day safety monitoring of the study, including the receipt, review, investigation, and follow-up of SAEs reported by the clinical study sites.

The Safety Monitoring Committee (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

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

1) Withdrawal of consent

2) Event which in the opinion of the investigator contraindicates further administration of investigational product such as illnesses or complications

3) Anaphylactic reaction to MEDI-563 (defined in Appendix 2)

Subjects who are permanently discontinued from investigational product will be followed for the full study period (through Study Day 168), including the collection of any protocol-specified blood specimens, unless consent is withdrawn.

4.8 Interruption or Discontinuation of Study Dosing and Randomization

If any of the following occur, no further administration of investigational product will take place and no further subjects will be randomized into the study:

1) Death in any subject in which the cause of death is assessed as possibly, probably, or definitely related to investigational product

2) Any anaphylactic event (defined in Appendix 2) or 2 serious allergic events judged related to investigational product.

3) Two infusion reactions judged related to the investigational product.

4) The occurrence of immune complex disease.

5) Events that, in the opinion of the medical monitor and the Safety Monitoring Committee (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/randomization 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 investigational product administration.

As with any MAb, allergic reactions and infusion reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be able to recognize and treat infusion reactions and allergic reactions such as anaphylaxis.

Infusion reactions usually occur within the first 24 hours after infusion and are characterized by a complex of symptoms that may include flu-like illness, fever, chills/rigors, nausea, urticaria, headache, bronchospasm, angioedema, hypotension, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock.

Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death (Sampson et al, 2006). See Appendix 2 for the clinical criteria for defining anaphylaxis.

If an anaphylactic or an infusion reaction occurs, the infusion will be stopped and a serum sample will be drawn for mast cell tryptase, histamine, TNF-alpha, and IL-1.

5 Statistical Considerations

5.1 General Considerations

All data will be provided in data listings sorted by treatment groups (MEDI-563 0.3 mg/kg, MEDI-563 1.0 mg/kg, or placebo), and visit number. Summary data will be presented in tabular format by treatment groups. 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. Statistical hypothesis testing, if appropriate, will be performed for the primary endpoint with a 2-sided test.

A comprehensive statistical analysis plan will be developed and approved prior to the database lock.

5.2 Sample Size and Power Calculations

5.2.1 Planned Sample Size

Sample size calculations have been performed for the primary endpoint of proportion of subjects with asthma exacerbations at Week 12 to allow for hypothesis testing. Sample size calculations are based on Fisher's exact test with alpha = 0.05 (2-sided) for testing the difference between the combined MED-563 treatment groups (n=72, 0.3 mg/kg and 1.0 mg/kg) and the combined placebo group (n=36). Assumptions include: (1) The proportion of placebo subjects with asthma exacerbations at Week 12 is 60% and (2) There will be ≥ 50%

reduction in the proportion of subjects with asthma exacerbations at Week 12 in the combined MEDI-563 (0.3 and 1.0 mg/kg) treatment groups. The sample size may be re-estimated using the proportion of subjects with asthma exacerbations (relapsed or de novo) up to the first interim analysis to preserve the power around 80% if the proportion of subjects with asthma exacerbations is different from the assumptions listed above.

There will be no adjustment on Type 1 error rate for sample size re-estimation in this study. However, the true overall type I error rate will be greater than 0.05 if the multiplicity adjustment is taken into account in the calculation. With 108 evaluable subjects, the statistical power to detect statistically significant differences in the proportion of subjects with asthma exacerbations at Week 12 in the combined MEDI-563 treatment groups and the placebo group will be 80% based on the above assumptions. Power calculations were performed using nQuery Advisor software program Version 6.01.

Table 5.2.1-1 and Table 5.2.1-2 present the probability of observing at least one infrequently occurring event when assuming a range of potential observed event rates and exact binomial 95% confidence intervals to assess the precision of estimates of the event rate for each individual treatment group (n=36) and combined MEDI-563 treatment group (n=72).

Table 5.2.1-1 Expected Number of Events and Probabilities of Observing at Least 1 or 2 Events Given the True Event Rates

N	True Event Rate (%)	Number of Events Expected	Probability of Observing at least 1 Event (%)	Probability of Observing at least 2 Events (%)
36	0.2	0	7.0	0.2
36	0.4	0	13.4	0.9
36	0.5	0	16.5	1.4
36	1.0	0	30.4	5.0
36	1.5	1	42.0	10.1
36	2.0	1	51.7	16.2
36	2.5	1	59.8	22.7
72	0.2	0	13.4	0.9
72	0.4	0	25.1	3.4
72	0.5	0	30.3	5.1
72	1.0	1	51.5	16.2
72	1.5	1	66.3	29.4

Table 5.2.1-1 Expected Number of Events and Probabilities of Observing at Least 1 or 2 Events Given the True Event Rates

N	True Event Rate (%)	Number of Events Expected	Probability of Observing at least 1 Event (%)	Probability of Observing at least 2 Events (%)
72	2.0	1	76.7	42.3
72	2.5	2	83.8	54.0

Table 5.2.1-2 Estimated Event Rates and 95% Exact Binomial Confidence Intervals Given the Number of Events Observed

N	Number of Events Observed	Estimated Event Rate (%)	95% Confidence Interval
36	0	0.0	(0.0%; 9.7%)
36	1	2.8	(0.1%; 14.5%)
36	2	5.6	(0.7%; 18.7%)
36	3	8.3	(1.8%; 22.5%)
72	0	0.0	(0.0%; 5.0%)
72	1	1.4	(0.0%; 7.5%)
72	2	2.8	(0.3%; 9.7%)
72	3	4.2	(0.9%; 11.7%)

5.2.2 Re-estimation of Sample Size

The sample size may be re-estimated based on the results of the first interim analysis as listed below. Examples of sample size estimates for the different assumptions are listed in Table 5.2.2-1.

- Sample size will be re-estimated if the proportion of subjects with asthma exacerbations (relapsed or de novo) at Week 12 is greater than or equal to 45% but less than 55%. Assumptions to re-estimate the sample size will be alpha = 0.05 (2-sided), current proportion of placebo subjects with asthma exacerbations, and a 50% reduction in the combined MEDI-563 groups.
- The sample size will not be re-estimated if the proportion of placebo subjects with asthma exacerbations (relapsed or de novo) through Week 12 is less than 45%.

- The study may be terminated if proportions of subjects with asthma exacerbations in the combined MEDI-563 groups at the interim analysis is approximately the same or lower than that in the placebo group.

Table 5.2.2-1 Possible Re-estimated Sample Sizes for Different Assumptions at First Interim Analysis

Placebo Proportion	MEDI-563 Proportion	N (Placebo)	N (MEDI-563)	Total Sample Size	Power (%)
0.540	0.270	43	86	129	80
0.500	0.250	49	98	147	81
0.450	0.225	57	114	171	80

5.3 Analysis Populations

All evaluable subjects will be included in the efficacy analyses. All randomized subjects, regardless of whether they are evaluable, will be included in the safety analyses. Missing data will be treated as missing without data imputation.

5.4 Primary Endpoint

The primary objective of this study is to evaluate the effect of two IV dose regimens of MEDI-563 (0.3 and 1.0 mg/kg) on the proportion of subjects with asthma exacerbations (relapsed or de novo) at Week 12 in adult subjects who required an urgent healthcare visit for treatment of an acute asthma exacerbation. The formula that will be used to evaluate the proportion of subjects with asthma exacerbations in the combined MEDI-563 treatment groups at Week 12 will be as follows:

- (Number of subjects with at least one asthma exacerbation in the combined MEDI-563 treatment groups [0.3 and 1.0 mg/kg] at Week 12) ÷ (Number of total evaluable subjects in the combined MEDI-563 treatment groups [0.3 and 1.0 mg/kg] at Week 12)

The Fisher's exact test will be performed for testing the differences in proportion of subjects with asthma exacerbations at Week 12 between the combined MEDI-563 treatment groups and the placebo group at an alpha level of 0.05.

The number of asthma exacerbations at Week 12 for each MEDI-563 treatment group (0.3 and 1.0 mg/kg) versus placebo will also be reported. The Fisher's exact test may be performed for testing this endpoint.

5.5 Secondary Endpoints

5.5.1 Safety Assessment

The safety of MEDI-563 in this subject population is a secondary objective of this study. Adverse events will be summarized categorically by system organ class, preferred term, severity, and relationship to investigational product through Study Day 84. Serious adverse events will be assessed through Study Day 84. Laboratory abnormalities, for tests such as serum CRP, ECP, and IL-6 levels will be evaluated in the MEDI-563 and placebo groups as changes from baseline.

5.5.2 Effect of MEDI-563 on the Proportion of Subjects with Asthma Exacerbations at Week 4

The formula in Section 5.4 will be used to explore the differences in the proportion of subjects with asthma exacerbations in each MEDI-563 treatment group (0.3 and 1.0 mg/kg) versus placebo and for the combined MEDI-563 treatment groups versus placebo at Week 4. The Fisher's exact test may be performed for testing this endpoint.

5.5.3 Effect of MEDI-563 on the Proportion of Subjects with Asthma Exacerbations at Week 24

The formula in Section 5.4 will be used to explore the differences in the proportion of subjects with asthma exacerbations in each MEDI-563 treatment group (0.3 and 1.0 mg/kg) versus placebo and for the combined MEDI-563 treatment groups versus placebo at Week 24. The Fisher's exact test may be performed for testing this endpoint.

5.5.4 Effect of MEDI-563 on Asthma Control

The ACQ is a 6-item subject reported questionnaire to assess the recall over the prior week with 6 items addressing night-time waking, symptoms on waking, activity limitation, shortness of breath, wheeze, and rescue short-acting beta agonist use. Questions are rated on a 7-point Likert scale from 0 (no impairment) to 6 (maximum impairment). Final scores are the mean of the 6 items and results in a score between 0, well controlled to 6, extremely poor controlled (Juniper 1999). Mean, mean change from baseline, and responder frequency tables will be provided. Individual subjects with score changes of -0.5 or less will be considered

responders. A change of -0.5 is considered to be a minimally important difference on the ACQ.

5.5.5 Effect of MEDI-563 on Variability of Airflow Obstruction

The analysis of the effect of MEDI-563 on variability of airflow obstruction (FEV_1 at the site and FEV_1 and PEF at home) through Study Day 84 will be primarily descriptive. Mean and mean change from baseline will be provided for office spirometry (FEV_1). Two-sample t-tests may be used to explore changes from baselines in subject FEV_1 between the combined MEDI-563 treatment groups and the placebo group.

5.5.6 Effect of MEDI-563 on Use of Concomitant Controller or Rescue Medications

The analysis of the effect of MEDI-563 on the need to use concomitant controller or rescue medications through Study Day 84 will be primarily descriptive.

5.5.7 Effect of MEDI-563 on Physician Global Assessment

The PGA will be summarized categorically.

5.5.8 Effect of MEDI-563 on Health-related Quality of Life

Health-related quality of life will be evaluated using the AQLQ(S). The overall score and the 4 domain scores (symptoms, activity limitations, emotional function and environmental stimuli) are the means of the responses to the questions in each of the domains. The analyses will be primarily descriptive. The mean, mean change from baseline, and responder frequency tables will be provided. Individual subjects with score changes of -0.5 or less will be considered responders. A change of -0.5 is considered to be a minimally important difference on the AQLQ(S).

5.5.9 Effect of MEDI-563 on Healthcare Utilization and Economics

The analysis of the effect of MEDI-563 on healthcare utilization and economics will be evaluated by summarizing the absolute number and proportion of healthcare resource utilization by resource type. The analyses will be primarily descriptive.

5.5.10 Assessment of PK and IM of MEDI-563

Individual MEDI-563 serum concentrations will be tabulated by treatment group along with descriptive statistics. Noncompartmental PK data analysis will be performed for MEDI-563 treated subjects, and descriptive statistics of these noncompartmental parameters will be provided. Due the limited sampling schedule, if the data allows, population PK data analysis may be performed to better characterize the PK of MEDI-563.

Immunogenicity results will be listed for each subject. Number and percentage of subjects who developed detectable anti-MEDI-563 antibodies will be summarized by treatment group (0.3 mg/kg, 1 mg/kg, or placebo). The impact of IM on PK will be assessed if data allows

5.6 Interim Analyses

There will be 2 interim analyses. The first interim analysis will be performed after at least 44 treated subjects have completed the Study Day 84 evaluations. The data will be used to re-estimate the sample size (see Section 5.2.2). The second interim analysis will be performed after all treated subjects have completed the Study Day 84 evaluations. The primary endpoint analysis described in Section 5.4 will be performed. Since the primary endpoint analysis for which this study is powered will be completed at the second interim analysis, it will not be repeated at the end of the study. All available primary endpoint data will be included in the interim analyses. In addition, analyses of limited secondary and exploratory endpoints (safety, asthma exacerbations, asthma control, and health related quality of life) will be included. These will be described in detail in the statistical analysis plan (SAP). Results from the interim analyses will be communicated to a limited number of MedImmune senior management independent of the clinical study team; these people will be identified in the unblinding plan before the interim analyses are performed. To ensure the blinding of each subject's treatment assignment throughout the study, the interim analyses will be performed by a limited number of MedImmune personnel (internal biostatisticians, programmers, and other personnel) not involved in the conduct of the study. MedImmune personnel associated with the conduct of the study, study site personnel, and subjects will remain blinded to the treatment assignment of individual subjects until the last subject completes the study and the database is locked.

6 Data Collection and Monitoring

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

Data recorded on source documents will be transcribed onto a validated data collection instrument (a paper case report form or electronic data screen) provided by MedImmune or designee. The investigator must ensure the accuracy and completeness of the data reported, and its consistency with the source documentation.

Data will be collected on all subjects who provide written informed consent. For subjects who fail the screening process, the following data will be collected:

1) Subject demographics
2) The reason the subject was not entered/randomized (ie, did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (eg, lost to follow-up, consent withdrawn)

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

Study documents (including subject records, copies of collected data, study notebook, and pharmacy records) must be kept secured in accordance with MedImmune policies and applicable regulatory requirements, 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, the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), Protection of Human Subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), and Investigational New Drug Application (21 CFR 312).

The protocol will be reviewed and approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of each participating center prior to study initiation. Serious adverse events 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 will explain the nature of the study and will inform the subject that participation is voluntary and that they can withdraw/can withdraw their child at any time. Written informed consent will be obtained from each subject prior to the screening procedures required for entry into the study. A copy of the signed consent form will be given to every subject 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 (SID) will be stored separately in another locked file cabinet. Study records may be maintained electronically and require the same security and confidentiality as paper. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by regulatory authorities or the sponsor of the clinical study. The principal investigator must also comply with all applicable privacy regulations (eg, Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

7.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

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/IEC's written unconditional approval of the study protocol, the informed consent form, and any other written materials to be provided to subjects will be in the possession of the investigator and the sponsor before the study is initiated. The IRB/IEC's unconditional approval statement will be transmitted by the investigator to the sponsor prior to shipment of investigational product supplies to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and the date of review.

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

The IRB/IEC must be informed by the principal investigator of informed consent form changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring through Study Day 84; 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.

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 informed 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 that the study involves research. They 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 of the subject, if the subject should

become pregnant) that are currently unforeseeable. They must also be informed of the study procedures to be followed and alternative treatment available to them. 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 or withdraw their child 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. They 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 study 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 subject, 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.

The original protocol ([redacted]) was amended on [redacted]. Major changes included removing the second dose of investigational product and shortening the study. Changes to the protocol are described in Appendix 6 and are incorporated in the body of Protocol Amendment 1.

Amendment 1 ([redacted]) was amended on [redacted]. Major changes included changing the venue from ED to urgent healthcare setting, increasing the number of sites, adding a 5 mg/mL formulation of MEDI-563 and matching placebo to be used in Canada, and clarifying the schedule of subject evaluations. An urgent healthcare setting for the purposes of this study may be an emergency department or an outpatient clinic equipped to provide the level of care specified in this protocol. Changes to the protocol are described in Appendix 6 and are incorporated in the body of Protocol Amendment 2.

Amendment 2 ([redacted]) was amended on [redacted]. Major changes included adding 3 follow-up phone calls after the last study visit to assess asthma exacerbations and to modify inclusion and exclusion criteria for clarification. Changes to the protocol are described in Appendix 6 and are incorporated in the body of Protocol Amendment 3.

Amendment 3 [redacted]) was amended on [redacted]. Major changes included adding spirometry/peak flow to screening in Table 3.5-1 (Schedule of Subject Evaluations); specifics about when interim analyses will be done; and to clarify re-estimation of sample size. Changes to the protocol are described in Appendix 6 and are incorporated in the body of Protocol Amendment 4.

11 References

Burney P, Potts J, Aït-Khaled N, et al. A multinational study of treatment failures in asthma management.Int J Tuberc Lung Dis. 2008; 12(1):13-8.

Green RH, Brightling CE, McKenna S, et al. Comparison of asthma treatment given in addition to inhaled corticosteroids on airway inflammation and responsiveness. Eur Respir J. 2006; 27(6):1144-51.

James AL, Elliot JG, Abramson MJ, Walters EH. Time to death, airway wall inflammation and remodelling in fatal asthma. Eur Respir J. 2005; 26(3):429-34.

Janson C, Herala M. Blood eosinophil count as a risk factor for relapse in acute asthma. Resp. Med 1992; 86: 101-104.

Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol. 1994; 47: 81-7.

Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest. May 1999; 115:1265-70.

Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J Oct 1999;14:902–7.

Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med 2005;99: 553–8.

Juniper EF, Bousquet J, Abetz L, et al. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med 2006; 100(6):616-24.

Masoli M, Fabian D, Holt S, Beasley R. The Global Burden of Asthma Report: Global Initiative for Asthma (GINA). www.ginasthma.org/report. 2004; 1-122.

Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. Eur Respir J. 2005; 26: 153-61.

Moorman JE, Rudd RA, Johnson CA, et al. Centers for Disease Control and Prevention (CDC). National surveillance for asthma--United States, 1980-2004.MMWR Surveill Summ. 2007; 56(8):1-54.

National Heart, Blood, and Lung Institute, National Asthma Education and Prevention Program. The Expert Panel Report 3 (EPR–3) Full Report 2007: Guidelines for the Diagnosis and Management of Asthma. 2007.

Restrepo RD, Peters J. Near-fatal asthma: recognition and management. Curr Opin Pulm Med. 2008; 14(1):13-23.

Romagnoli M, Caramori G, Braccioni F, et al; ENFUMOSA Study Group. Near-fatal asthma phenotype in the ENFUMOSA Cohort.Clin Exp Allergy. 2007; 37(4):552-7.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006; 117(2):391-7.

Ulrik CS, Frederiksen J. Mortality and markers of risk of asthma death among 1,075 outpatients with asthma. Chest. 1995 ;108(1):10-5.

Van den Toorn LM, Overbeek SE, de Jongste JC, Leman K, Hoogsteden HC, Prins JB. Airway inflammation is present during clinical remission of atopic asthma. Am J Respir Crit Care Med. 2001; 164:2107-13.

Appendix 1 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

Quick Reference

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE grading table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

General Instructions

Estimating Severity Grade

If the need arises to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located at the top of Page 3. For AEs that are not listed in the table but will be collected systematically for a study/trial, protocol teams are highly encouraged to define study-specific severity scales within the protocol or an appendix to the protocol. (Please see "Template Wording for the Expedited Adverse Event Reporting Section of DAIDS-sponsored Protocols".) This is particularly important for laboratory values because the "Estimating Severity Grade" category only applies to clinical symptoms.

Grading Adult and Pediatric AEs

The DAIDS AE grading table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the table. If there is no distinction in the table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

Determining Severity Grade

If the severity of an AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

Definitions

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young Children Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	Adult Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

Contents

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6 C	38.7 – 39.3 C	39.4 – 40.5 C	> 40.5 C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	> 140 – 159 mmHg systolic OR > 90 – 99 mmHg diastolic	> 160 – 179 mmHg systolic OR > 100 – 109 mmHg diastolic	> 180 mmHg systolic OR > 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay **– Pediatric ≤ 16 years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) **– Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) **– Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **– Pediatric < 18 years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, 1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin (Hgb)				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *1.32 – 1.55 mmol/L*	7.5 – 8.4 g/dL *1.16 – 1.31 mmol/L*	6.50 – 7.4 g/dL *1.01 – 1.15 mmol/L*	< 6.5 g/dL *< 1.01 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *1.55 – 1.69 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *0.39 – 0.53 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *0.54 – 0.68 mmol/L*	7.0 – 8.9 g/dL *1.09 – 1.39 mmol/L* OR Any decrease ≥ 4.5 g/dL *≥ 0.69 mmol/L*	< 7.0 g/dL *< 1.09 mmol/L*
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *1.32 – 1.46 mmol/L*	7.0 – 8.4 g/dL *1.09 – 1.31 mmol/L*	6.0 – 6.9 g/dL *0.93 – 1.08 mmol/L*	< 6.00 g/dL *< 0.93 mmol/L*

* Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *1.47 – 1.63 mmol/L*	8.0 – 9.4 g/dL *1.24 – 1.46 mmol/L*	7.0 – 7.9 g/dL *1.09 – 1.23 mmol/L*	< 7.00 g/dL *< 1.09 mmol/L*
Infant*†, 1 – 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *1.86 – 2.02 mmol/L*	10.0 – 11.9 g/dL *1.55 – 1.85 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L*	< 9.0 g/dL *< 1.40 mmol/L*
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*
CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN

* Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high (corrected for albumin)				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low (corrected for albumin)				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*

* Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*

* Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
URINALYSIS	***Standard International Units are listed in italics***			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

* Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

Appendix 2 Clinical Criteria for Defining Anaphylaxis

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

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

AND AT LEAST ONE OF THE FOLLOWING

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

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

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

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

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

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

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

3) 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.

Appendix 3 National Heart, Blood, and Lung Institute Classification of Asthma Severity

The table below is from National Heart, Blood, and Lung Institute, National Asthma Education and Prevention Program. The Expert Panel Report 3 (EPR–3) Full Report 2007: Guidelines for the Diagnosis and Management of Asthma. 2007: page 74.

FIGURE 3–4c. CLASSIFYING ASTHMA SEVERITY IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

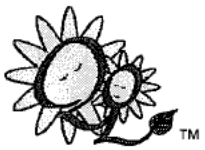
- **Classifying severity for patients who are not currently taking long-term control medications.**

Components of Severity		Classification of Asthma Severity (Youths ≥12 years of age and adults)			
			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 >1x/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			

- 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.

Appendix 4 Asthma Control Questionnaire

ASTHMA CONTROL QUESTIONNAIRE (ACQ)



For further information:

[redacted]
Professor
[redacted]
PO18 8NA, England
Telephone: [redacted]
Fax: [redacted]
E-mail: [redacted]
Web [redacted]

MAY 1997

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

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

Subj Initials _ _ _

ASTHMA CONTROL QUESTIONNAIRE© | SELF-ADMINISTERED

Please answer questions 1 - 6.

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

1. On average, during the past week, how often were you **woken by your asthma** during the night?

0 Never
1 Hardly ever
2 A few times
3 Several times
4 Many times
5 A great many times
6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?

0 No symptoms
1 Very mild symptoms
2 Mild symptoms
3 Moderate symptoms
4 Quite severe symptoms
5 Severe symptoms
6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?

0 Not limited at all
1 Very slightly limited
2 Slightly limited
3 Moderately limited
4 Very limited
5 Extremely limited
6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?

0 None
1 A very little
2 A little
3 A moderate amount
4 Quite a lot
5 A great deal
6 A very great deal

ASTHMA CONTROL QUESTIONNAIRE© SELF-ADMINISTERED

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

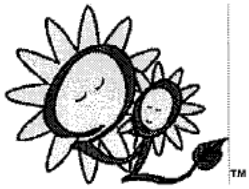
To be completed by a member of the clinic staff

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

Appendix 5 Asthma Quality of Life Questionnaire

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

SELF-ADMINISTERED



For further information:

[redacted]
Professor
[redacted]
Telephone: [redacted]
Fax: [redacted]
E-mail: [redacted]
Web: [redacted]

JUNE 1998

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

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

Subj Initials _ _ _

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) | SELF-ADMINISTERED

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

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

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

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

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

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

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

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

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

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

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

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) SELF-ADMINISTERED

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

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

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

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

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

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

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) SELF-ADMINISTERED

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

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

DOMAIN CODE:

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

Appendix 6 Summary of Amendments to the Protocol

Protocol Amendment 1; [redacted]

All text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. Major changes to the protocol are described below.

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

2) The potential number of participating sites was increased from approximately 5 sites in the US to up to 10 sites in North America. This change is to facilitate enrollment.

3) The study was shortened to accommodate the ED population. Subjects will only receive one dose of investigational product and be followed for 84 days. This follow-up period is more than 5 half-lives of MEDI-563. In addition, since the primary endpoint of the study is asthma exacerbation rate at Week 12, one dose of investigational product should be adequate to evaluate the differences between treatment groups. Changes were made throughout the protocol to accommodate this change.

4) The study visit schedule was changed to accommodate the reduction in study duration. Subjects will be evaluated at the study site on Study Day 0, Study Day 7; Study Day 42; and Study Day 84. Subjects will be contacted by telephone on Study Day 28 and Study Day 63. Based on data from MI-CP158, this schedule is adequate to evaluate safety and efficacy. Changes were made to the study design, study flow diagram, and study schedule.

5) The 0.1 mg/kg dose of investigational product was changed to 0.3 mg/kg. This change was made to ensure adequate drug coverage throughout the study period.

6) Study objectives 2 (evaluate the effect of MEDI-563 on the time to the first asthma exacerbation after dosing) and 4 (evaluate the effect of MEDI-563 on the asthma exacerbation rate at Week 26) were removed because the reduction in study duration makes them not applicable. The corresponding endpoints were removed from the statistical section.

7) Study treatment initiation was changed from prior to being discharged from the hospital or ED to within 7 days of meeting eligibility criteria. This change was made because many subjects wanted more time to think about participating in the study. It should not affect the evaluation of the primary endpoint. This change affected the study design section and concomitant medications (ie, prednisone).

8) The following inclusion criteria were changed to facilitate enrollment in the study.

   - Inclusion criterion Number 1 was changed. The maximum age of subjects at time of dosing was changed from 55 to 60 years old. This change was made to broaden the subject population. Other eligibility criteria will eliminate subjects with COPD.

- Inclusion criterion Number 6 was removed. Subjects will not be required to use a short acting bronchodilator as rescue medication prior to the current ED visit. This change was made because many subjects do no have the resources available to provide the rescue medication.
- Inclusion criterion Number 8 was changed. Subjects could have been treated with inhaled bronchodilators for the current asthma exacerbation in the ED or by EMS. This change was made because some subjects are treated by EMS at least one time prior to getting to the ED.
- Inclusion criterion Number 9 was changed. FEV_1 was changed from at least 30% and not more than 65% predicted to at least 30% and not more than 70% predicted. The original selection of 65% was relatively arbitrary. The criterion for nonresponsiveness and consideration for inpatient admission is typically 70% predicted.
- Inclusion criterion Number 14 was removed. Many subjects do not have the resources available to provide asthma controller medications, and this is the target population for this study.

9) Exclusion criterion Number 18 was divided into 2 exclusion criteria. Exclusion criterion Number 18 excludes subjects who have received a diagnosis of COPD by a health professional and criterion Number 24 excludes subjects with a history of cigarette smoking > 20 pack years.

10) An exclusion criterion was added to exclude subjects who previously received MEDI-563.

11) Blood samples for hepatitis A, B, and C will not be collected. Results from these samples were being used to determine if subjects could receive the second IV infusion on Study Day 56.

12) Basophils, eosinophil derived proteins, and eotaxin will also be blinded as these values could be a source of unblinding.

13) The investigational product administration section was changed to add specifics about flushing the IV tubing after the infusion.

14) Legal representative was removed from protocol language. This was removed because subjects who are unable to decide to be in the protocol themselves will not be included.

15) MEDI-563 concentrations will be evaluated in serum, not plasma. Text was changed accordingly.

16) The manufacturer of MEDI-563 and placebo were removed from the protocol as more specific details about this are provided in the CTM manual.

17) Home peak flow monitoring procedures were clarified.

18) Clarifications were made throughout protocol text for consistency.

Protocol Amendment 2; [redacted]

All text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. Major changes to the protocol are described below.

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

2) Nonclinical and clinical experience sections of the protocol were updated with current information.

3) The potential number of participating sites was increased from up to 10 sites in North America to approximately 15-20 sites in North America. This change is to facilitate enrollment.

4) The ED was changed to urgent healthcare setting. An urgent healthcare setting for the purposes of this study may be an emergency department or an outpatient clinic equipped to provide the level of care specified in this protocol. This change was made to facilitate enrollment.

5) The 5 mg/mL formulation of MEDI-563 was added to the protocol. Sites in Canada will use only the 5 mg/mL formulation. Sites in the USA may use the 5 mg/mL or the 50 mg/mL formulation. This change was made to allow for enrollment in Canada.

6) Informed consent procedures were clarified. Informed consent will be obtained once the subject is considered clinically stable by the investigator.

7) Statements were added for clarification purposes to the schedule of events. Procedures completed as part of the assessment and treatment of the asthma exacerbation may be used for screening, even though these may occur prior to informed consent. This is to avoid repeating blood draws, spirometry, and other assessments for eligibility purposes.

8) The screening/Study Day 0 visit was split into 2 separate visits. This is for clarification. Subjects may be dosed up to 7 days after the asthma exacerbation.

9) Blood sample collection was clarified. Samples for screening hematology, chemistry, and the urinalysis will be sent to the local laboratory. Samples for Study Day 0 hematology, chemistry, and the urinalysis will be sent to the central laboratory, even if on the same day as screening.

10) Many of the blood samples were moved to Study Day 0 (ie, IgE, ECP, IL-6, CRP, anti-MEDI-563 antibodies, possible analysis of interleukins, eosinophil derived proteins, and eotaxin). These will be collected once eligibility has been established and prior to investigational product administration.

11) A urine ßHCG and a physical examination were added on Study Day 0 because some subjects may not receive the investigational product on the same day as screening.

12) RNA transcripts (PAXgene™ tubes) and biomarker analysis (serum sample) were added on Study Day 0 and Study Day 84.

13) Evaluable subjects were defined as those who receive the investigational product and are followed according to the protocol through Study Day 42. This change was made because of the change in study schedule from Amendment 1. Subjects will only have a phone evaluation 4 weeks after investigational product administration.

Protocol Amendment 3; [redacted]

All text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3. Major changes to the protocol are described below.

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

2) Nonclinical section was updated.

3) A secondary objective was added to evaluate the effect of MEDI-563 on the asthma exacerbation rate (relapse or de novo) at Week 24. This change was made to gather additional data about asthma exacerbations after treatment with MEDI-563. The change was made in the objectives and in the statistical section.

4) Three additional phone contacts were added (Study Day 112, 140, and 168) to assess asthma exacerbations beyond the last study visit on Study Day 84. This change was made to gather data needed for the additional secondary objective listed above. The change was made to the study design and study schedule.

5) Study Day 84 was change to Study Day 168 where appropriate throughout the protocol. The only assessments made after Study Day 84 will be for asthma exacerbations.

6) Inclusion and Exclusion criterion were clarified as follows:

   a) Inclusion criterion Number 8 was changed to allow for PEF or spirometry. This change was made because study sites often do PEF, not spirometry as part of the standard of care.

   b) Inclusion criterion Number 8 was further changed to remove the requirement of at least 30%. This was moved to inclusion criterion Number 14 and is now: Investigator has determined the subject is clinically stable and $FEV_1 \geq 30\%$ predicted prior to dosing with investigational product. This change was made for clarification purposes; subjects must have an FEV_1 of at least 30% predicted on Study Day 0 in order to receive the investigational product.

   c) Inclusion criterion Number 12 was changed to a normal for an asthmatic population and excludes alternative diagnosis per the investigator.

   d) Exclusion criterion Number 7 was changed to allow travel outside of the US and Canada as long as it was not to a location where parasite infestations are prevalent within the last year. This change was made for clarification.

   e) Exclusion criterion Number 21 was clarified. Subjects who had a known exposure to inhaled occupational agents or fumes with an established diagnosis of occupational asthma will be excluded.

   f) Exclusion criterion Number 26 was added. Subjects with asthma exacerbations due to acute inhalation exposure will be excluded.

7) Instructions for vital signs were clarified throughout the protocol. During and immediately after administration of investigational product a 5 minute window will be acceptable per protocol.

8) The blinding section was clarified. In the event an investigator needs to be unblinded, they are to follow procedures contained in the IXRS manual.

9) There may be two interim analyses. The first may be after at least 40% of treated subjects have completed the Study Day 84 evaluations and the second may be after all treated subjects have completed the Study Day 84 evaluations. Information about the interim analyses was added to the blinding section and the statistical section.

10) The sample size may be re-estimated using the proportion of subjects with asthma exacerbation (relapsed or de novo) after the first interim analysis if the proportion is different from the assumptions used in the sample size calculation.

Protocol Amendment 4; [redacted]

All text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 4. Major changes to the protocol are described below.

1) The Study Abstract was updated to be consistent with changes in the body of the protocol.
2) Table 3.5-1 (Schedule of Subject Evaluations) was updated to include either spirometry or peak flow at screening.
3) Asthma exacerbation rate was changed to proportion of subjects with asthma exacerbations throughout the protocol. This change was made for consistency.
4) Section 5.2 (Sample Size and Power Calculations) - Sample size re-estimation was changed in response to Health Canada. Details are provided about when and how the sample size will be re-estimated. No adjustments for Type 1 error rate will be made.
5) Section 5.6 (Interim Analyses) was changed. There will be 2 interim analyses. Details about these interim analyses were provided.