A Phase 2b, Randomized Study to Evaluate the Efficacy and Safety of Subcutaneous MEDI-528 in Adults with Uncontrolled Asthma

Sponsor Protocol Number: MI-CP198/D3290L00001

Application Number: IND 11478

Investigational Product: MEDI-528

Sponsor: MedImmune LLC, a wholly-owned subsidiary of AstraZeneca
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Protocol, Date: Original Protocol, [redacted]
Amendment 1, [redacted]
Amendment 2, [redacted]

Sponsor Agreement:

[redacted], whose signature is on file at MedImmune, is authorized to sign the protocol on behalf of the sponsor.

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 any applicable laws and requirements and any conditions required by a Regulatory Authority and/or an Independent Ethics Committee/Institutional Review Board.

The protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authorities and Institutional Review Boards/Independent Ethics Committees (IRBs/IECs), and must be approved by the IRB/IEC prior to their implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature_____ Date _____

Investigator Name and Title_____
(please print)

Investigator Affiliation, City, State/Province_____

_____
(please print)

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List of Abbreviations

Abbreviation	Definition
ACQ	Asthma Control Questionnaire
AE	adverse event
AHR	airway hyperresponsiveness
AQLQ(S)	Asthma Quality of Life Questionnaire
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
ATP	According-to-Protocol
ATS/ERS	American Thoracic Society/European Respiratory Society
BMI	body mass index
BUN	Blood urea nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRF	case report form
DTT	Dithiothreitol
ECG	Electrocardiogram
ECLA	electrochemiluminescent assay
ED	emergency department
ELISA	enzyme-linked immunosorbent assay
EPR	Expert Panel Report
ePRO	electronic Patient-reported Outcome
EU	European Union
FDA	Food and Drug Administration
FEIA	fluorescence enzyme immunoassay
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
hCG	human chorionic gonadotropin

Abbreviation	Definition
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPF	high power field
HRQOL	Health-related quality of life
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
IEC	Independent Ethics Committee
IL-9	Interleukin-9
IM	Immunogenicity
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
IVRS	interactive voice response system
MAb	monoclonal antibody
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No-observed-adverse-effect level
PBS	phosphate buffered saline
PD	Pharmacodynamics
PD_{15}	provoking dose to cause a 15% fall in FEV_1
PEF	peak expiratory flow
PK	Pharmacokinetics
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SC	Subcutaneous
SID	subject identification
Th2	T helper cell type 2
WBC	white blood cell

Study Abstract

TITLE

A Phase 2b, Randomized Study to Evaluate the Efficacy and Safety of Subcutaneous MEDI-528 in Adults with Uncontrolled Asthma

OBJECTIVES

The primary objective of this study is to evaluate the effect of multiple-dose subcutaneous (SC) administration of MEDI-528 on asthma control in adults with uncontrolled, moderate-to-severe, persistent asthma.

The secondary objectives of this study are:

1) To evaluate the safety and tolerability of MEDI-528 in this subject population;
2) To evaluate the effect of MEDI-528 on asthma exacerbations;
3) To further assess the effect of MEDI-528 on asthma control;
4) To evaluate the effect of MEDI-528 on pulmonary function;
5) To determine the effect of MEDI-528 on health-related quality of life (HRQOL); and
6) To assess the pharmacokinetics (PK) and immunogenicity (IM) of MEDI-528.

The exploratory objectives of this study are:

1) To determine the effect of MEDI-528 on healthcare utilization and productivity;
2) To evaluate the pharmacodynamics (PD) of MEDI-528 in blood and serum (ie, number and activation state of pulmonary mast cells and numbers and airway epithelium [mucus production]); and
3) To identify biomarkers for this subject population of moderate-to-severe asthmatics during a steroid-stable and steroid-reduction phases.

STUDY DESIGN

This is a Phase 2b, randomized, double-blind, placebo-controlled, parallel group, multicenter study. Approximately 75 sites worldwide will participate in the study. Approximately 320 subjects will be randomized in a ratio of 1:1:1:1 to 1 of 4 treatment groups to receive MEDI-528 or placebo as follows:

- Treatment Group 1: SC MEDI-528 30 mg (N=80)
- Treatment Group 2: SC MEDI-528 100 mg (N=80)
- Treatment Group 3: SC MEDI-528 300 mg (N=80)
- Treatment Group 4: SC Placebo (N=80)

Investigational product (MEDI-528 [100 mg/mL] or placebo) will be administered as 4 injections with 0.3 mL of investigational product for the first injection and 1 mL of investigational product for each subsequent injection every 2 weeks for 24 weeks on Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169. Thereafter, subjects will be followed for an additional 154 days after treatment (Day 323).

A 28-day screening/run-in period will precede administration of investigational product. During the 28-day screening/run-in period, subjects will standardize their fluticasone/salmeterol or budesonide/formoterol dose. The treatment period will be divided into 2 phases: steroid-stable and steroid-reduction. From Day 1 through Day 92, subjects will continue to receive stable doses of fluticasone/salmeterol or budesonide/formoterol (ie, steroid-stable phase). After Day 92, subjects may begin fluticasone/salmeterol or budesonide/formoterol reduction.

Subjects will be in the study for about 351 days (28 days for screening/run-in, 169 days of treatment, and 154

days for follow-up, which is approximately 5 half-lives of the investigational product).

SUBJECT POPULATION

Adult male or female subjects with uncontrolled, moderate-to-severe, persistent asthma.

TREATMENT

Subjects will receive investigational product (MEDI-528 [30, 100, or 300 mg] or placebo) every 2 weeks for 24 weeks on Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169.

ASSESSMENT OF ENDPOINTS

The primary endpoint is the change from baseline in the mean ACQ score at Day 92

Comparisons between individual MEDI-528 treatment groups (30 mg, 100 mg, or 300 mg) and placebo will be conducted. An analysis of covariance (ANCOVA) model will be tested using a 2-sided test. The model will include the change from baseline in the mean ACQ score at Day 92 as the dependent variable. The model will also include the treatment groups (MEDI-528 treatment groups vs placebo), atopic asthma status, and geographic region (pooled centers) as independent factors. The mean ACQ score at baseline will be included as a covariate in the model. An additional factor may be included in the model to adjust for use of concomitant asthma controller medications.

The secondary endpoints will be analyzed to assess the safety; effect of MEDI-528 on asthma exacerbations, asthma control, pulmonary function, and health-related quality of life; and PK and IM of MEDI-528.

Other exploratory assessments may include, but are not limited to, gene array, proteomics, and tryptase measurements from whole blood samples and proteomics (both cells and fluid), [redacted]. These data will be summarized using descriptive statistics by treatment group.

INTERIM ANALYSIS

Two interim analyses are planned for this study. The first interim analysis will analyze the primary endpoint, which is the change from baseline in the mean ACQ score at Day 92. The second interim analysis will analyze the secondary endpoints at Day 176. The first interim analysis will be conducted after all subjects have completed the Day 92 evaluations. The second interim analysis will be conducted after all subjects have completed the Day 176 evaluations.

The first interim analysis will be conducted after all subjects have completed the Day 92 evaluations. The primary endpoint analysis will constitute the first interim analysis. Since the primary endpoint analysis for which this study is powered will be completed at the first interim analysis, it will not be repeated at the end of the study. As such there is no need for multiplicity adjustment of the Type I error.

The second interim analysis will be conducted after all subjects have completed the Day 176 evaluations. Evaluation of asthma exacerbation will constitute the second interim analysis.

Analyses of safety data available at the time of data cut-off will be presented in the interim analyses. If necessary, analyses of limited secondary endpoints may be included in the interim analyses. The interim analyses will be described in detail in the statistical analysis plan. If changes to the clinical development plan occur, only changes that affect individuals involved in the clinical conduct of the study will be communicated (ie, the actual data of the interim analyses will not be communicated).

There will be no adjustment for any covariates, multiple comparisons or center (block) effect in this multicenter study. P-values will be provided without multiplicity adjustment.

SAMPLE SIZE AND POWER CALCULATIONS

Approximately 240 subjects are required for the study. Assuming a drop-out rate of about 20% in the study a total of 320 randomized subjects are expected to provide 240 subjects for the study.

Sample size estimations have been performed for the primary endpoint of change from baseline in the mean

ACQ score at Day 92 in adult subjects with uncontrolled, moderate-to-severe, persistent asthma.

It is assumed that the change from baseline in the mean ACQ score at Day 92 will be -0.4 to -0.5 and -0.9 to -1.1 for the placebo and each MEDI-528 treatment group, respectively, with a common standard deviation of 0.8 to 1.0. With approximately 60 subjects in each treatment group (a total of 240 subjects), the statistical power for detecting a statistically significant difference in the change from baseline in the mean ACQ score at Day 92 will be between 58% and 99% based on the above assumptions and a 2-sided t-test with Type I error of $\alpha = 0.05$ and 0.10 and a randomization ratio of 1:1:1:1. Assuming a drop-out rate of about 20% in the study, a total of 320 randomized subjects are expected to provide 240 subjects for the study. The 320 subjects will be randomized at a ratio of 1:1:1:1 to 1 of 4 treatment groups to receive MEDI-528 or placebo every 2 weeks for 24 weeks, with approximately 80 subjects randomized to each treatment group (3 MEDI-528 treatment groups and placebo).

1 Introduction

1.1 Disease Background

Asthma affects 8.5% of children and 6.7% of adults in the United States of America (USA; Moorman, 2007). Approximately 1.8 million people with asthma visited the emergency department (ED) in 2004; this is an ED visit rate of 64 per 10,000 people. In the same year, there were 497,000 asthma hospitalizations. An average of 4,210 deaths from asthma occurred annually from 2001 through 2003. The annual cost of asthma is estimated to be nearly $18 billion (Asthma and Allergy Foundation, 2000). Despite the use of long-acting bronchodilators and inhaled corticosteroids (ICS), asthma exacerbations continue to be a major source of morbidity worldwide (Masoli et al, 2004).

Most patients with asthma have mild-to-moderate disease that is usually controlled by regular use of inhaled corticosteroids combined with short-acting β2-adrenoceptor agonists for relief of symptoms. However, in a small subset of patients (approximately 10% of the asthmatic population) asthma continues to be poorly controlled in terms of ongoing symptoms, frequent exacerbations, persistent and variable airway obstruction and frequent requirement for β2-agonists despite aggressive treatment. This results in considerable impact on quality of life, disproportionate use of healthcare resources, and adverse effects from regular systemic steroid use. There is therefore a significant medical need for new improved alternative treatments in the poorly-controlled asthma patient population, including new biological agents.

1.2 Description of MEDI-528

MEDI-528 is a fully humanized immunoglobulin G1 kappa monoclonal antibody (MAb) derived by humanization and in vitro affinity maturation of MH9A3, a murine anti-human interleukin-9 (IL-9) MAb. MEDI-528, also named 7F3com-2H2, is approximately 6-fold more potent than the parent antibody MH9A3 in a cell-based IL-9 neutralization assay. In addition, MEDI-528 binds to human IL-9 with approximately 5-fold higher affinity compared with the murine antibody MH9A3, and its specificity is preserved (no detectable binding to murine IL-9). MEDI-528 is composed of 2 heavy chains and 2 light chains and has a molecular weight of approximately 148,400 Daltons (Da).

1.3 Nonclinical Experience with MEDI-528

Neutralization of IL-9 activity has been shown to reduce the airway inflammation and increased AHR seen in animal models of asthma. MEDI-528 is a fully humanized immunoglobulin G1 kappa MAb that binds specifically to IL-9 with high affinity and may modulate the biological effects of this cytokine. MEDI-528 may represent a new long-term maintenance or controller therapy for symptomatic, persistent asthma.

MEDI-528 has been evaluated in a 26-week toxicology study in cynomolgus monkeys. In this study, MEDI-528 was administered once weekly via subcutaneous (SC) injection to cynomolgus monkeys for a total of 27 doses at dose levels of 0, 50, and 100 mg/kg/dose. No MEDI-528-related changes were observed in any of the evaluated parameters up to and including the highest dose of 100 mg/kg. Based on the lack of adverse effects, the no observed adverse effect level (NOAEL) of MEDI-528 in cynomolgus monkeys after 27 once-weekly SC injections is at least 100 mg/kg/dose.

Nonclinical safety studies have also been performed using a surrogate murine anti-IL-9 monoclonal antibody (referred to as MM9C1) to evaluate the toxicity and toxicokinetics of MM9C1 (9.99 and 49.72 mg/kg) when administered weekly for 26 weeks (27 total doses) to BALB/c mice. Treatment-related microscopic inflammation of the subcutis was localized to the skin injection sites in males and females given 9.99 and 49.72 mg/kg/dose. Reversibility of the inflammatory changes was evidenced by decreased severity and incidence of this finding in mice at the recovery sacrifice interval. On the basis of the observed reversibility of injection site inflammation following 6 weeks of recovery, the NOAEL of MM9C1 when administered weekly via SC injection to male and female mice for 26 weeks is at least 49.72 mg/kg/dose.

Further information on nonclinical studies of MEDI-528 can be found in the Investigator's Brochure.

1.4 Clinical Experience with MEDI-528

Six clinical studies have been conducted using MEDI-528, 2 studies in healthy volunteers (MI-CP105 and MI-CP109) and 4 studies in adult subjects with asthma (MI-CP131, MI-CP138, MI-CP139, and MI-CP143). Both healthy volunteer studies are complete, and data analysis is ongoing in the 4 asthma studies. Studies MI-CP139 and MI-CP143 were terminated prematurely.

To date, the majority of adverse events (AEs) were mild in severity and there were no dose-limiting toxicities. No deaths, dose-limiting toxicities, or evidence of immune complex disease occurred in any subject treated with MEDI-528 (or placebo). There was one related serious adverse event (SAE) occurring in a subject treated with multiple SC doses of 50 mg of MEDI-528 in Study MI-CP143 [abnormal brain magnetic resonance imaging (MRI)]. The subject had a 6 x 4 mm left sided pontine hyperintensity noted on the Day 28 MRI that was not present at baseline. The investigator considered the event possibly related to study drug. However, a repeat MRI with gadolinium contrast showed no abnormal findings or pontine hyperintensity. No other significant changes in the central nervous system were observed as assessed using brain MRI or focused neurological examinations. No significant changes occurred in electrocardiograms (ECG) and no elevations in troponin levels were observed. In MI-CP105, transient, isolated elevations in pancreatic enzyme levels were seen in 2 volunteers (3.0 mg/kg IV).

Further information on clinical studies of MEDI-528 can be found in the Investigator's Brochure.

1.5 Rationale for Study

Neutralization of IL-9 activity has been shown to reduce the airway inflammation and increased AHR seen in animal models of asthma. MEDI-528 is a humanized immunoglobulin G1 kappa MAb that binds specifically to IL-9 with high affinity and may modulate the biological effects of this cytokine.

The primary clinical goal of asthma management is to optimize asthma control (minimization of symptoms, activity limitation, bronchoconstriction, and rescue β2-agonist use) and thus reduce the risk of life-threatening exacerbations and long-term morbidity. The Asthma Control Questionnaire (ACQ) was developed to meet these goals (see Section 5.3.11.1). In this study, ACQ will be used as the primary efficacy endpoint to measure both the adequacy of asthma control and change in asthma control as a result of MEDI-528 treatment (see Section 7.3.1).

The purpose of this Phase 2b study is to evaluate the efficacy and safety of multiple fixed SC doses of MEDI-528 (30, 100, or 300 mg) on asthma control in adults with uncontrolled, moderate-to-severe, persistent asthma.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to evaluate the effect of multiple-dose SC administration of MEDI-528 on asthma control in adults with uncontrolled, moderate-to-severe, persistent asthma.

2.2 Secondary Objectives

The secondary objectives of this study are:

1) To evaluate the safety and tolerability of MEDI-528 in this subject population;
2) To evaluate the effect of MEDI-528 on asthma exacerbations;
3) To further assess the effect of MEDI-528 on asthma control;
4) To evaluate the effect of MEDI-528 on pulmonary function;
5) To determine the effect of MEDI-528 on health-related quality of life (HRQOL); and
6) To assess the PK and IM of MEDI-528.

2.3 Exploratory Objectives

The exploratory objectives of this study are:

1) To determine the effect of MEDI-528 on healthcare utilization and productivity;
2) To evaluate the pharmacodynamics (PD) of MEDI-528 in blood and serum (ie, number and activation state of pulmonary mast cells and numbers and airway epithelium [mucus production]); and
3) To identify biomarkers for this subject population of moderate-to-severe asthmatics during a steroid-stable and steroid-reduction phases.

3 Study Design

3.1 Overview of Study Design

This is a Phase 2b, randomized, double-blind, placebo-controlled, parallel group, multicenter study to evaluate the efficacy and safety of multiple-dose SC administration of MEDI-528 in adult subjects with uncontrolled, moderate-to-severe, persistent asthma. Approximately 75

sites worldwide will participate in the study. Approximately 320 subjects will be randomized in a ratio of 1:1:1:1 to 1 of 4 treatment groups to receive MEDI-528 or placebo as follows:

- Treatment Group 1: SC MEDI-528 30 mg (N=80)
- Treatment Group 2: SC MEDI-528 100 mg (N=80)
- Treatment Group 3: SC MEDI-528 300 mg (N=80)
- Treatment Group 4: SC Placebo (N=80)

Investigational product (MEDI-528 [100 mg/mL] or placebo) will be administered as 4 injections with 0.3 mL of investigational product for the first injection and 1 mL of investigational product for each subsequent injection every 2 weeks for 24 weeks on Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169. Thereafter, subjects will be followed for an additional 154 days after treatment (Day 323).

A 28-day screening/run-in period will precede administration of investigational product. During the 28-day screening/run-in period, subjects will standardize their fluticasone/salmeterol or budesonide/formoterol dose as described in Section 4.6.1. The treatment period will be divided into 2 phases: steroid-stable and steroid-reduction. From Day 1 through Day 92, subjects will continue to receive stable doses of fluticasone/salmeterol or budesonide/formoterol (ie, steroid-stable phase) as described in Section 4.6.2.1. After Day 92, subjects may begin fluticasone/salmeterol or budesonide/formoterol reduction (or oral steroid dose reduction if receiving chronic doses of oral steroids) as described in Section 4.6.2.2 (ie, steroid-reduction phase).

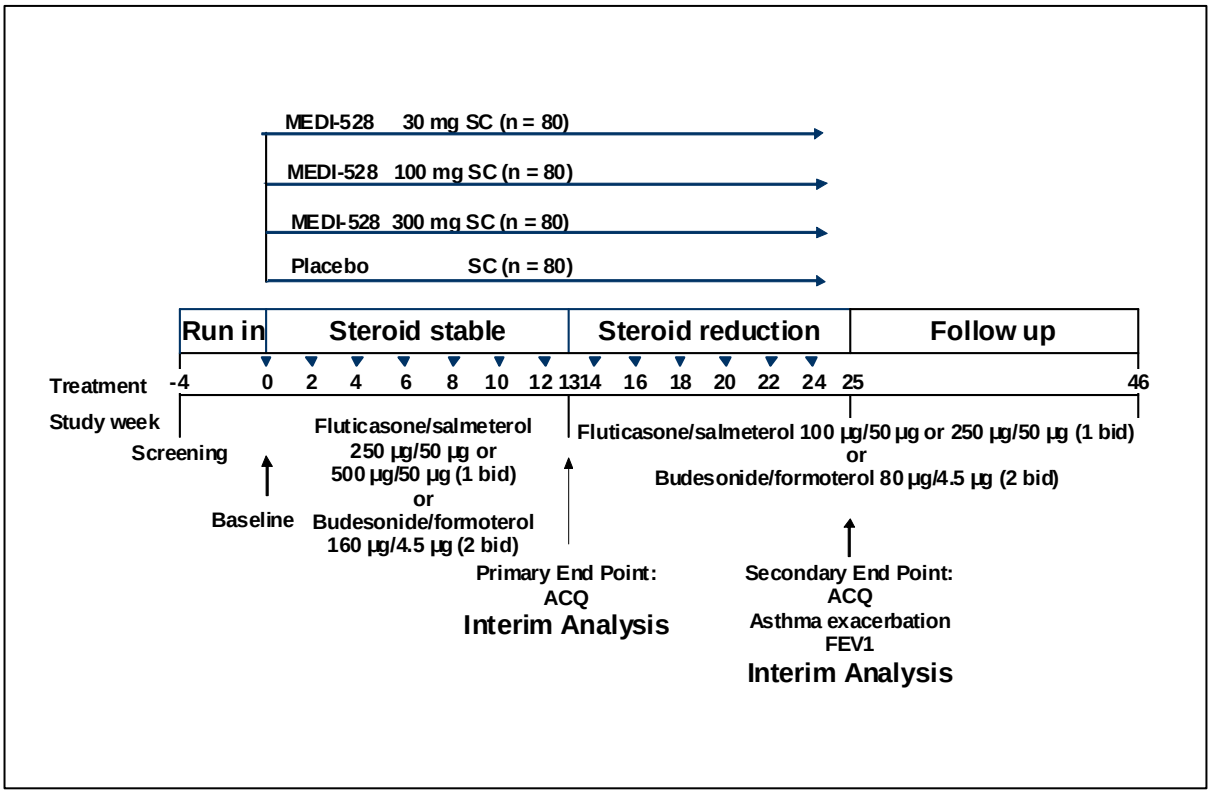

Figure 3.1-1 Study Flow Diagram

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

3.2 Estimated Study Duration

Subjects will be in the study for about 351 days (28 days for screening/run-in, 169 days of treatment, and 154 days for follow-up, which is approximately 5 half-lives of the investigational product).

4 Study Procedures

4.1 Subject Participation and Identification

Study participation begins once written informed consent is obtained (see Section 10.3 for details). Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice system, IVRS), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID

number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomized), including the reason(s) for screening failure (see Section 9.1 for details).

4.2 Subject Selection

The subjects in this study will be adult male or female subjects with uncontrolled, moderate-to-severe, persistent asthma.

The investigator (physician) or qualified designee will discuss the study with a subject who is considered a potential candidate for the study and provide the subject with the study-specific informed consent form approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). 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 any locally required authorization (eg, Health Insurance Portability and Accountability Act [HIPAA] authorization in the USA, European Union [EU] Data Privacy Directive authorization in the EU), will be obtained prior to conducting any protocol-related procedures, including screening evaluations or medication washouts. See Section 10.3 for additional details concerning informed consent.

4.2.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1) Male or female
2) Age 18 through 65 years at the time of screening
3) Written informed consent and any locally required authorization (eg, HIPAA in the USA, EU Data Privacy Directive in the EU, obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
4) Female subjects of childbearing potential who are sexually active with non-sterilized male partner must use adequate contraception from screening through the end of the study. An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing

hormones are included, the recommended methods of contraception are described in Table 4.2.1-1. Sustained abstinence is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception

a) Non-sterilized males who are sexually active with a female of child-bearing potential must use adequate contraception (see Table 4.2.1-1) from screening through the end of the study

Table 4.2.1-1 Recommended Methods of Contraception

Barrier Methods	Intrauterine Devices (IUDs)	Hormonal Contraceptives
Male condom plus spermicide Cap (plus spermicidal cream or jelly) plus male condom Diaphragm (plus spermicidal cream or jelly) plus male condom	Copper T Progesterone T plus condom or spermicide	Implants Hormone shot/injection Combined pill Minipill Patch

b) Females or female partners not of childbearing potential must have been surgically sterilized (eg, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or postmenopausal (defined as at least 1 year since last regular menses)

c) Sterilized males must be at least 1-year post vasectomy and have obtained documentation of the absence of sperm in the ejaculate

5) Weight ≥ 45 kg but ≤ 120 kg (ie, ≥ 100 lb but ≤ 265 lb) and body mass index (BMI) between 18 and 35 kg/m^2

6) Physician-diagnosed asthma by medical chart

7) Currently taking ICS or is a candidate to receive ICS per Expert Panel Report (EPR)-3 (National Heart, Lung, and Blood Institute, 2007)

8) Pre-bronchodilator forced expiratory volume in 1 second (FEV_1) value ≥ 40% at Day -28 and Day 1

9) A post-bronchodilator increase in FEV_1 and/or FVC ≥ 12% and ≥ 200 mL at Day -28 OR meeting any one of the following criteria:

a) Proof of post-bronchodilator reversibility of airflow obstruction ≥ 12% documented within 36 months prior to randomization or proof of a positive response [PC_{20} ≤ 8 mg/mL (ATS, 2000)] to a methacholine challenge documented within 36 months prior to randomization; OR

b) Proof of partial reversibility of ≥ 8% to < 12% improvement in post-bronchodilator FEV_1 on Day -28 and achievement of ≥ 12% reversibility at a second time between Day -27 and Day -15; OR

c) If a) and b) are not met and all other inclusion/exclusion criteria are met, subjects with a FEV_1 of ≥ 1.5 L and ≥ 60% on Day -14 will be eligible to undergo a methacholine challenge. If the subject achieves a positive response to this methacholine challenge (PC_{20} ≤ 8 mg/mL), then this criterion is met

10) Uncontrolled asthma consistent with EPR-3. In the 28 days before screening, subjects should have a history of one or more of the following:

- Daytime asthma symptoms ≥ 2 days/week
- Nighttime awakening ≥ 1 night/week
- Albuterol/salbutamol use ≥ 2 days/week

11) An ACQ score ≥ 1.5 at Day -28 and at Day 1 (ACQ is described in Section 5.3.11.1). Subject may be re-screened one additional time if they met this criterion at Day -28 but failed to meet it at Day 1 (procedure described in Section 4.6.1)

12) At least one asthma exacerbation in the 12 months before screening that required intake of systemic corticosteroids after an unscheduled medical encounter or as agreed with a physician based on an asthma action plan that defines when oral steroids can be taken by the subject

13) Ability and willingness to complete the follow-up period through Day 323 as required by the protocol.

4.2.2 Exclusion Criteria

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

1) Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results

2) Concurrent enrollment in another clinical study

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

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

5) History of anaphylaxis to other biologic therapy

6) Lung disease other than asthma (eg, chronic obstructive pulmonary disease [COPD], cystic fibrosis)

7) Severe depression as measured by a depression score > 15 on the Hospital Anxiety and Depression Scale (HADS; see Appendix 7) at either Day-28 or Day 1.

8) History of suicidal behavior in the previous 3 years as measured by the Columbia Suicide Severity Rating Scale (C-SSRS; see Appendix 8 [Baseline C-SSRS]) at Day -28.

9) Acute illness other than asthma at the screening and randomization visits

10) History of an active infection within 28 days before and during the screening period, or evidence of clinically significant active infection, including ongoing chronic infection

11) History of ingestion of untreated water in a location known to be infected with parasites, resulting in acute or chronic diarrhea; history of recent travel to areas where parasite infestations are endemic within 6 months before screening; or a diagnosis of parasitic infection within 6 months before screening

12) Use of immunosuppressive medication (except oral prednisone up to a dose of 20 mg every other day or equivalent [eg, 10 mg a day or 5 mg twice a day] and inhaled and topical corticosteroids) within 28 days before randomization

13) Receipt of immunoglobulin or blood products within 28 days before randomization

14) Plans to donate blood during the entire study period

15) Donated blood or has had a blood transfusion within 28 days before screening

16) Receipt of any non-biological study drugs or interventional therapy (including surgical procedures) within 28 days of the first dose of investigational product in this study

17) Receipt of any biologicals including MEDI-528 within 5 half-lives before the first dose of investigational product in this study

18) History of any known immunodeficiency disorder

19) A positive hepatitis B surface antigen, or hepatitis C virus antibody, as determined by medical history and/or subject's verbal report

20) A positive human immunodeficiency virus test or is taking antiretroviral medications, as determined by medical history and/or subject's verbal report

21) A live attenuated vaccination received within 28 days before screening

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

23) Breastfeeding or lactating

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

25) History suggestive of COPD or of tobacco smoking ≥ 10 pack-years

26) Evidence of any uncontrolled systemic disease upon physical examination

27) History of cancer, apart from basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy ≥ 1 year before Day 1 or other malignancies treated with apparent success with curative therapy ≥ 5 years before screening

28) Any noninfectious disease involving multiple organs (eg, cystic fibrosis, systemic lupus erythematosus, hemophilia, multiple sclerosis, etc.) that, in the opinion of the

investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results

29) Individuals who are legally institutionalized

4.3 Treatment Assignment

An IVRS will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. A subject is considered randomized into the study when the investigator notifies the IVRS that the subject meets eligibility criteria and the IVRS provides the assignment of a blinded investigational product kit number to the subject.

Subjects will be randomized at a 1:1:1:1 ratio to receive either MEDI-528 or placebo. The randomization will be stratified by asthma status (atopic or nonatopic) and fluticasone/salmeterol dose (250 μg/50 μg or 500 μg/50 μg) or budesonide/formoterol dose (160 μg/4.5 μg). Randomization into the nonatopic asthma strata will be restricted to a maximum of 160 subjects to ensure that at least 160 subjects (at least 40 subjects in each treatment group) with atopic asthma are randomized in the study. The placebo and each MEDI-528 treatment group will have the same number of subjects in the fluticasone/salmeterol 250 μg/50 μg strata or budesonide/formoterol 160 μg/4.5 μg strata and fluticasone/salmeterol 500 μg/50 μg strata.

The procedure for using IVRS is as follows:

- The investigator or designee contacts the IVRS and provides the SID number and subject's baseline characteristic(s) used to verify that it is the same subject
- The IVRS assigns a treatment arm and investigational product kit number(s) to the subject
- Confirmation of this information is sent to the investigator/designee who dispenses the investigational product to the subject per the communication and records the appropriate information in the subject's medical records and investigational product accountability log.

Investigational product (MEDI-528 or placebo) must be administered the same day the investigational product kit number(s) is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the MedImmune study monitor and/or its designee must be notified immediately.

4.4 Blinding

This is a double-blind study. Subjects and study site personnel, including the investigators, study nurses, coordinators, and monitors or others conducting study assessments will be blinded to treatment allocation. As MEDI-528 will be visually distinct from placebo, the investigational product will be handled by an unblinded Investigational Product Manager (a pharmacist or study nurse). Investigational product will be administered by the Investigational Product Manager or a different study team member who will not be involved in any other part of the clinical or study management of the subjects. An unblinded drug monitor will perform drug accountability and to ensure that adequate levels of MEDI-528 and placebo are maintained at the site through the IVRS.

The vendor for packaging and labeling of the clinical supplies, designated IVRS personnel, the unblinded Investigational Product Manager at the MedImmune Clinical Research Pharmacy Service, and the unblinded drug monitor are the only individuals who will have access to information that may identify a subject's treatment allocation. 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.

In an emergency, the investigator will have the ability to become unblinded. Any unblinding due to an emergent safety issue will be performed according to the IVRS manual.

Biostatisticians, programmers, external data facilitators, PK and PD scientists, and a limited number of MedImmune personnel, independent of the clinical study team conducting this study who will analyze interim data may be unblinded (see Section 7.4). The results of the interim analyses will be communicated with only limited numbers of MedImmune Senior Management personnel, independent of the clinical study team conducting the study, will be identified on the unblinding plan before the interim analysis is performed.

Investigational product will be supplied to the site in coded kits identical in appearance. Each kit and vial will have a unique number printed on the labels. Detailed instructions are in the Investigational Product Manual supplied by MedImmune.

4.5 Study Treatment

4.5.1 Investigational Product (MEDI-528 and Placebo)

Investigational product will be distributed to clinical sites using designated distribution centers. The sponsor will provide the investigator(s) with adequate quantities of investigational product. MEDI-528 and placebo will be manufactured and supplied by MedImmune. MEDI-528 (100 mg/mL) and placebo will be supplied as clear to slightly opalescent, sterile solutions at a pH of 6.0. All vials of study drugs will be stored in a secured refrigerator at +2°C to +8°C (36°F to 46°F) and will not be frozen.

MEDI-528: MEDI-528 will be supplied in 3 mL vials filled with 1 mL solution of MEDI 528 at a concentration of 100 mg/mL, 10 mM histidine buffer, and 150 mM sodium chloride, pH 6.

Placebo: Placebo will be supplied in 3 mL vials filled with 1 mL solution containing 10 mM histidine buffer, 150 mM sodium chloride, and 0.02% (w/w) Polysorbate-80 (Tween-80), pH 6.

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

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to the sponsor. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune (refer to the Investigational Product Manual or other written instructions provided by MedImmune or its designee for contact information and specific shipping instructions).

4.5.2 Treatment Regimens

Approximately 320 subjects will be randomized in a ratio of 1:1:1:1 to 1 of 4 treatment groups to receive investigational product (MEDI-528 [30, 100, or 300 mg] or placebo) as described in Table 4.5.2-1. Subjects will receive investigational product every 2 weeks for 24 weeks on Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169. A total of 4 injections of investigational product will be given at each dosing visit. MEDI-528 will be

provided in 100 mg/mL concentrations. Each subject will receive a 0.3-mL injection of investigational product for the first injection and a 1-mL injection of investigational product for each subsequent injection.

Table 4.5.2-1 Treatment Regimen

Treatment Group	N	Treatment Regimen [a]
MEDI-528 30 mg	80	1 × 0.3 mL SC MEDI-528; 3 × 1 mL SC Placebo
MEDI-528 100 mg	80	1 x 0.3 mL SC Placebo; 1 × 1 mL SC MEDI-528; 2 × 1 mL SC Placebo
MEDI-528 300 mg	80	1 x 0.3 mL SC Placebo; 3 × 1 mL SC MEDI-528
Placebo	80	1 x 0.3 mL SC Placebo; 3 × 1 mL SC Placebo

[a]Subjects will receive either MEDI-528 or placebo every 2 weeks for 169 days on Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169. A total of 52 injections will be administered during the study.

4.5.3 Investigational Product Preparation and Administration

Investigational product will be injected into the SC tissue of the triceps muscle of each arm using a 26-gauge 3/8-inch needle. The person administering the dose will wipe the skin surface of the arm with alcohol and allow to air dry. The skin over the triceps muscle (excluding the muscle) will be pinched to isolate the SC tissue from the muscle. The needle will be inserted at a 90-degree angle approximately halfway into the SC tissue. The investigational product will be slowly injected (at least a 5-second duration is recommended) into the SC tissue using gentle pressure. The area should not be massaged after injection. All subjects will receive a total of 4 injections of investigational product at every dosing visit.

The dose of investigational product for administration must be prepared by the site's designated investigational product manager using aseptic technique and should be equilibrated to room temperature prior to administration. Detailed instructions regarding investigational product preparation can be found in the Investigational Product Manual that will be provided to the investigator's or site's designated investigational product manager.

The day of receipt of the first dose of investigational product is considered Day 1.

Vital signs (blood pressure, temperature, pulse rate, and respiration rate) will be obtained before and within 5 minutes and every 30 minutes (± 5 minutes) after investigational product administration for a minimum of 2 hours (± 5 minutes) or until stable, whichever is later for the first 3 administration visits (ie, Days 1, 15, and 29). During subsequent administrations visits, vital signs will be obtained before and within 5 minutes and every 30 minutes

(± 5 minutes) after investigational product administration for a minimum of 1 hour (± 5 minutes) or until stable, whichever is later.

4.5.4 Concomitant Medications

All concomitant medications given to the subject from Day -28 through Day 323 will be recorded on the source document.

During the screening/run-in period and throughout the study, subjects will be given fixed doses of fluticasone/salmeterol or budesonide/formoterol and rescue albuterol/salbutamol MDI as described in Section 4.6.

Subjects are allowed to take any medications for asthma control deemed medically necessary by the investigator. This includes inhaled corticosteroids, short- and long-acting β2-agonists, leukotriene modifiers, theophylline, or inhaled cromones. Subjects may take oral corticosteroids for treatment of acute asthma exacerbations (see Appendix 3 for definition of asthma exacerbation).

The following medications are considered exclusionary and are not permitted during the study. The sponsor must be notified if a subject receives any of these during the study.

1) Immunosuppressive medication (except oral prednisone or equivalent up to 20 mg every other day and inhaled and topical corticosteroids) within 28 days before randomization
2) Investigational agents or use of any biologicals including omalizumab within 28 days before the first dose of investigational product in this study or within 5 half lives of an investigational agent or biologic
3) New allergy vaccination (immunotherapy) within 28 days before randomization or a change in dose of allergy vaccination during the study (subjects will not be excluded if receiving maintenance dose of allergy vaccination)
4) A live or attenuated vaccination received within 28 days before screening.

4.5.5 Treatment Compliance

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

Fluticasone/salmeterol or budesonide/formoterol use during the screening/run-in period and throughout the study will be monitored by study site personnel via return of empty medication vials.

4.6 Steroid Reduction Schedule and Asthma Exacerbation Management

Management of corticosteroid use (ICS and systemic) and asthma exacerbation (as defined in Appendix 3) are described in Table 4.6-1.

Table 4.6-1 Steroid Reduction Schedule and Asthma Exacerbation Management

	Steroid Reduction Schedule			
	Screening/Run-in (Day -28 through Day -1)	**Steroid-stable (Day 1 through Day 92)**	**Steroid-reduction (Day 93 through Day 176)**	**Follow-up (Day 177 through Day 323)**
Fluticasone/ salmeterol Dose for Moderate or Severe Persistent Asthma	250 µg/50 µg or 500 µg/50 µg	250 µg/50 µg or 500 µg/50 µg	100 µg/50 µg or 250 µg/50 µg	100 µg/50 µg or 250 µg/50 µg
Budesonide/ formoterol Dose for Moderate Persistent Asthma	160 µg/4.5 µg	160 µg/4.5 µg	80 µg/4.5 µg	80 µg/4.5 µg
Exacerbation Management	Screen failure	One exacerbation: Systemic corticosteroid burst + hospitalization if necessary + continue on the same fluticasone/ salmeterol or budesonide/ formoterol dose ≥2 exacerbations: Systemic corticosteroid burst + hospitalization if necessary + fluticasone/ salmeterol 500 µg/50 µg or continue on the same budesonide/ formoterol dose	Systemic corticosteroid burst +hospitalization if necessary + pre-exacerbation dose of fluticasone/ salmeterol or budesonide/ formoterol	Systemic corticosteroid burst + hospitalization if necessary + pre-exacerbation dose of fluticasone/ salmeterol or budesonide/ formoterol

4.6.1 28-day Screening/Run-in Period

A 28-day screening/run-in period will be used to standardize the subjects' fluticasone/salmeterol or budesonide/formoterol dose in the study. During the 28-day

screening/run-in period, subjects will use fluticasone/salmeterol 250 µg/50 µg or 500 µg/50 µg one inhalation twice-a-day or budesonide/formoterol 160 µg/4.5 µg two inhalations twice-a-day (see Appendix 10 for trade names), depending on severity, one inhalation twice-a-day, plus albuterol/salbutamol MDI for reliever medication. Oral corticosteroids will be discontinued during the screening/run-in period.

Subjects who are not currently taking long-term control medications at screening will receive fluticasone/salmeterol 250 µg/50 µg or budesonide/formoterol 160 µg/4.5 µg for moderate persistent asthma or fluticasone/salmeterol 500 µg/50 µg for severe persistent asthma, respectively (Appendix 11).

Subjects who have uncontrolled asthma (asthma that is not well controlled or very poorly controlled [Appendix 12]) taking low to medium daily dose ICS will receive fluticasone/salmeterol 250 µg/50 µg or budesonide/formoterol 160 µg/4.5 µg and subjects who have uncontrolled asthma taking high daily dose ICS will receive fluticasone/salmeterol 500 µg/50 µg, respectively (Appendix 13).

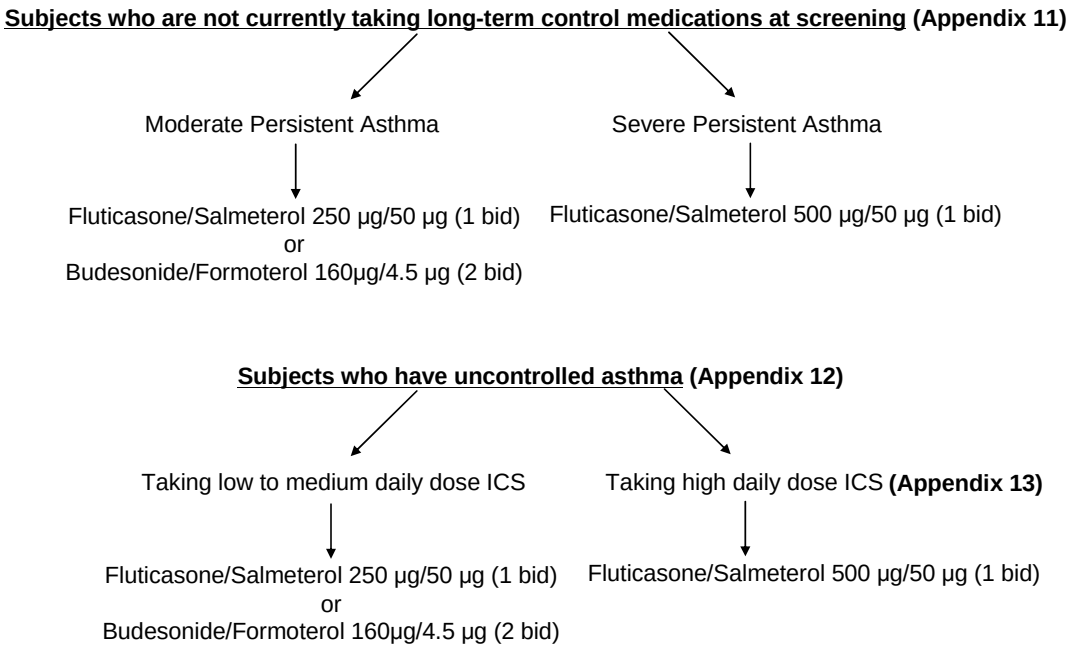

Figure 4.6.1-1 Flow Diagram of Fluticasone/salmeterol or Budesonide/formoterol Dose Selection

If an asthma exacerbation (as defined in Appendix 3) occurs during the screening/run-in period, the subject will not be randomized into the study. At the end of the screening/run-in

period, subjects who continue to have an ACQ score of ≥ 1.5 will be randomized into the study. A subject who met the ACQ eligibility criterion at Day -28 but failed to meet it at Day 1 may be re-screened at least 28 days after the subject failed to meet the Day 1 ACQ eligibility criterion. If the subject meets the ACQ eligibility criterion at that time, the subject can be randomized into the study.

4.6.2 Treatment Period

4.6.2.1 Steroid-stable Phase

The steroid-stable phase will start on Day 1 and continue through Day 92. During the steroid-stable phase, subjects will remain on the same dose of fluticasone/salmeterol (250 μg/50 μg or 500 μg/50 μg) or budesonide/formoterol (160 μg/4.5 μg) started during the screening/run-in period. Subjects may receive fluticasone/salmeterol or budesonide/formoterol before receiving investigational product on dosing days.

However, if an asthma exacerbation occurs during the steroid-stable phase:

- Subjects will receive systemic corticosteroids burst therapy
- Subjects will continue on the same dose of fluticasone/salmeterol or budesonide/formoterol as before the asthma exacerbation
- The subject may be hospitalized in addition to receiving systemic corticosteroids burst therapy.

If a subject has ≥ 2 asthma exacerbations during the steroid-stable phase:

- Subjects will receive systemic corticosteroids burst therapy
- Subjects will receive fluticasone/salmeterol 500 μg/50 μg or the same dose of budesonide/formoterol as before the asthma exacerbation
- The subject may be hospitalized in addition to receiving systemic corticosteroids burst therapy.

If after discharge from the hospital, the subject's asthma remains unstable and prevents the subject from going into the steroid-reduction phase, the subject should remain at the same steroid dose.

4.6.2.2 Steroid-reduction Phase

The steroid-reduction phase will start on Day 93 and continue through Day 176. During this steroid-reduction phase, subjects with clinically stable asthma (no additional medical care or medication within 28 days during the steroid-stable phase) will attempt to reduce their fluticasone/salmeterol or budesonide/formoterol dose.

Subjects with clinically stable asthma will begin to reduce their fluticasone/salmeterol or budesonide/formoterol dose at Day 93. Subsequent reductions will only occur if the subject's asthma remains clinically stable as follows:

- Subjects receiving fluticasone/salmeterol 250 μg/50 μg will receive 100 μg/50 μg
- Subjects receiving budesonide/formoterol 160 μg/4.5 μg will receive 80 μg/4.5 μg
- Subjects receiving fluticasone/salmeterol 500 μg/50 μg will receive 250 μg/50 μg.

If an asthma exacerbation occurs, the subject will be hospitalized (if necessary) and will receive systemic corticosteroids burst therapy followed by the last fluticasone/salmeterol or budesonide/formoterol dose during the steroid-stable phase. Subjects unable to tolerate a steroid reduction will remain at their current dose.

If a subject has ≥ 2 asthma exacerbations during the steroid-reduction phase:

- Subjects will receive systemic corticosteroids burst therapy
- Subjects will receive fluticasone/salmeterol 500 μg/50 μg or budesonide/formoterol 160 μg/4.5 μg
- The subject may be hospitalized in addition to receiving systemic corticosteroids burst therapy.

If after discharge from the hospital, the subject's asthma remains unstable and prevents the subject from going into the steroid-reduction phase, the subject should remain at the same steroid dose.

4.6.3 Follow-up Period

During the follow-up period, subjects will continue to receive the same dose of fluticasone/salmeterol or budesonide/formoterol.

If an asthma exacerbation occurs, the subject will be hospitalized (if necessary) and will receive systemic corticosteroids burst therapy followed by the last fluticasone/salmeterol or budesonide/formoterol dose during the steroid-reduction phase.

If a subject has ≥ 2 asthma exacerbations during the follow-up period, subjects will be treated the same as a subject who has experienced ≥ 2 asthma exacerbations during the steroid-reduction phase.

4.7 Subject Status

Subject Completion

An individual subject will be considered to have completed the study if the subject was followed up through the end of the study, defined as Day 323, regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if one of the following conditions applies:

- Withdrawal of consent: If consent for follow-up is withdrawn, the subject will not receive any further investigational product or further study observation. Note that the subject may need to undergo additional tests or tapering of treatment to withdraw safely.
- Lost to follow-up: Subjects will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status on Day 323.

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

Permanent Discontinuation of Investigational Product

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment (Section 6.4.1).

4.8 Study Completion

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

5 Assessment of Efficacy and Clinical Pharmacology

5.1 Efficacy and Clinical Pharmacology Parameters

Efficacy parameters include the following:

- ACQ
- Asthma exacerbations
- Patient Global Impression of Severity
- Time to first improvement in asthma control
- Fluticasone/salmeterol or budesonide/formoterol use
- Systemic steroid use
- Use of controller medications and rescue medications
- Asthma symptom scores
- Pulmonary function tests to include measurement of airflow limitation via FEV_1 and forced vital capacity (FVC) and morning peak expiratory flow (PEF)
- Asthma Quality of Life Questionnaire (AQLQ[S])
- IgE-fluorescence enzyme immunoassay (FEIA)

Clinical pharmacology parameters include the following:

- PK parameters
- Anti-MEDI-528 antibodies
- PD markers

5.2 Schedule of Study Procedures

All subjects who are assigned an SID number 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 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 if medical evaluation is needed and the urgency of the situation permits. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the investigator and made available to the sponsor or designee during monitoring visits.

A schedule of study procedures is presented in Table 5.2-1 (Screening and Treatment Periods) and Table 5.2-2 (Follow-up Period), followed by a description of each visit. A description of the study procedures is included in Section 5.3.

Table 5.2-1 Schedule of Study Procedures - Screening and Treatment Periods

	Screening/ Run-in		Treatment Period														
			Steroid-stable Phase (Days 1-92)								Steroid-reduction Phase (Days 93-176)						
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Day	**-28**	**-14**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**92**	**99**	**113**	**127**	**141**	**155**	**169**	**176**
Written informed consent and appropriate privacy act document authorization/Assignment of SID number	X																
Hospital Anxiety and Depression Scale	X		X		X		X		X		X		X		X		X
Columbia Suicide Severity Rating Scale	X																
Medical and asthma history	X																
Chest x-ray	X																
Reversibility of FEV_1 or	X																
Methacholine challenge, if applicable		X															
Spirometry	X	X	X		X		X		X	X	X	X	X	X	X	X	X
Physical examination including weight and neurological examination	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X									X							X

Table 5.2-1 Schedule of Study Procedures - Screening and Treatment Periods

	Screening/ Run-in		Treatment Period														
			Steroid-stable Phase (Days 1-92)								Steroid-reduction Phase (Days 93-176)						
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Day	**-28**	**-14**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**92**	**99**	**113**	**127**	**141**	**155**	**169**	**176**
Hepatitis A, B, C, HIV-1, HIV-2 testing	X																
IgE-FEIA antibody test	X															X	
Serum chemistry, hematology, and urinalysis	X		X		X		X		X			X				X	
Troponin			X													X	
Safety biomarkers			X														
Serum βHCG	X																
Urine βHCG			X	X	X	X	X	X	X		X	X	X	X	X	X	
MEDI-528 serum concentration			X	X	X		X		X				X			X	X
Anti-MEDI-528 antibodies			X		X		X		X				X			X	X
Sputum collection (at selected sites)			X							X							X
Whole blood for RNA analysis			X							X							X
Asthma exacerbations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review home peak flow, use of rescue medications, and Asthma Symptom Scores	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review ACQ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5.2-1 Schedule of Study Procedures - Screening and Treatment Periods

	Screening/ Run-in		Treatment Period														
			Steroid-stable Phase (Days 1-92)								Steroid-reduction Phase (Days 93-176)						
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Day	**-28**	**-14**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**92**	**99**	**113**	**127**	**141**	**155**	**169**	**176**
Review AQLQ(S)			X		X		X		X			X		X			X
Review Patient Global Impression of Severity			X		X		X		X			X		X			X
Healthcare utilization				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Work Productivity and Activity Impairment Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess injection sites			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense fluticasone/salmeterol or budesonide/formoterol	X		X		X		X		X	X			X				
Verify eligibility criteria	X		X														
Randomization			X														
Investigational product administration			X	X	X	X	X	X	X		X	X	X	X	X	X	

Table 5.2-2 Schedule of Study Evaluations - Follow-up Period

	Follow-up Period				
Visit	**18**	**19**	**20**	**21**	**Visit 22/Day 323 End of Study/ Discontinuation**
Day	**204**	**232**	**260**	**288**	
Spirometry	X		X		X
Physical examination including weight and neurological examination	X	X	X	X	X
Vital Signs	X	X	X	X	X
ECG			X		X
IgE-FEIA antibody test					X
Serum chemistry, hematology, and urinalysis			X		X
Troponin					X
Urine βHCG			X		X
MEDI-528 Serum Concentration	X	X	X	X	X
Anti-MEDI-528 Antibodies	X		X		X
Assessment of AEs/SAEs	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Dispense fluticasone/salmeterol or budesonide/formoterol	X	X	X	X	

5.2.1 Screening

All screening procedures must be performed within 28 days before first dose of investigational product (Day 1). The screening evaluations may be carried out over more than one visit but within a maximum of 3 days. Written informed consent and any locally required authorization (eg, HIPAA in the USA, EU Data Privacy Directive authorization in the EU) must be obtained prior to performing any study-related procedure, including screening evaluations.

Screening Day -28

Visit 1

1) Obtain written informed consent and appropriate privacy act document authorization, if applicable
2) Assign an SID number
3) Verify eligibility criteria

4) Assess mood and behavior using HADS and C-SSRS
5) Perform medical and asthma history
6) Obtain chest x-ray if no evidence of radiological assessments within the previous 12 months
7) Reversibility of FEV_1 (subjects with a documented history of reversibility must still attempt to reverse at this visit)
8) Perform spirometry
9) Perform physical examination including weight and neurological examination
10) Take vital signs
11) Perform ECG
12) Collect blood for screening samples:
    - Hepatitis A, B, C, human immunodeficiency virus (HIV)-1, HIV-2
    - Serum chemistry
    - Hematology
    - Serum βHCG (for females of childbearing potential only)
    - IgE-FEIA antibody test
13) Collect urine for urinalysis
14) Measure asthma exacerbations
15) Home peak flow, use of rescue medications, and asthma symptom scores
16) Administer ACQ
17) Administer Work Productivity and Activity Impairment Questionnaire
18) Assess for AEs and SAEs
19) Record concomitant medications
20) Dispense fluticasone/salmeterol or budesonide/formoterol

Screening Day -14 ± 2

Visit 2

1) Perform spirometry
2) Perform methacholine challenge, if applicable
3) Take vital signs
4) Assess for AEs and SAEs
5) Record concomitant medications

6) Measure asthma exacerbations

7) Review home peak flow, use of rescue medications, and asthma symptom scores

8) Review ACQ

9) Administer Work Productivity and Activity Impairment Questionnaire

5.2.2 Treatment Period

Day 1: First Dose

Visit 3

1) Verify eligibility criteria

2) Assess mood and behavior using HADS

3) Spirometry

4) Perform physical examination including weight and neurological examination (if applicable, record new findings as AEs or SAEs)

5) Collect blood for baseline samples:

- Serum chemistry (including amylase and lipase)
- Troponin
- Hematology
- Safety biomarkers
- MEDI-528 serum concentration
- Anti-MEDI-528 antibodies
- Whole blood for RNA analysis

6) Collect urine for urinalysis

7) Collect urine for pregnancy test; ensure result is negative (for females of childbearing potential only)

8) Collect sputum (at selected sites)

9) Measure asthma exacerbations

10) Review home peak flow, use of rescue medications, and asthma symptom scores

11) Review ACQ

12) Review AQLQ(S)

13) Review Patient Global Impression of Severity

14) Review Work Productivity and Activity Impairment Questionnaire

15) Assess for AEs and SAEs

16) Update concomitant medications

17) Dispense fluticasone/salmeterol or budesonide/formoterol

18) Randomize and assign investigational product kit number

19) Take vital signs before administration of investigational product

20) Administer investigational product

21) Take vital signs within 5 minutes and every 30 minutes (± 5 minutes) after investigational product administration for a minimum of 2 hours (± 5 minutes) or until stable, whichever is later

22) Assess injection sites

23) Assess for AEs and SAEs

24) Record concomitant medications

Day 15 ± 2: Second Dose

Visit 4

1) Perform physical examination including weight and neurological examination

2) Collect blood:

   - MEDI-528 serum concentration

3) Collect urine for pregnancy test; ensure result is negative (for females of childbearing potential only)

4) Measure asthma exacerbations

5) Review home peak flow, use of rescue medications, and asthma symptom scores

6) Review ACQ

7) Assess healthcare utilization

8) Review Work Productivity and Activity Impairment Questionnaire

9) Assess for AEs and SAEs

10) Assess injection sites

11) Update concomitant medications

12) Take vital signs before administration of investigational product

13) Administer investigational product

14) Take vital signs within 5 minutes and every 30 minutes (± 5 minutes) after investigational product administration for a minimum of 2 hours (± 5 minutes) or until stable, whichever is later

15) Assess for AEs and SAEs

16) Update concomitant medications

Day 29 ± 2: Third Dose

Visit 5

1) Assess mood and behavior using HADS

2) Spirometry

3) Perform physical examination including weight and neurological examination

4) Collect blood:

- Serum chemistry
- Hematology
- MEDI-528 serum concentration
- Anti-MEDI-528 antibodies

5) Collect urine for urinalysis

6) Collect urine for pregnancy test; ensure result is negative (for females of childbearing potential only)

7) Measure asthma exacerbations

8) Review home peak flow, use of rescue medications, and asthma symptom scores

9) Review ACQ

10) Review AQLQ(S)

11) Review Patient Global Impression of Severity

12) Assess healthcare utilization

13) Review Work Productivity and Activity Impairment Questionnaire

14) Assess for AEs and SAEs

15) Assess injection sites

16) Update concomitant medications

17) Take vital signs before administration of investigational product

18) Administer investigational product

19) Take vital signs within 5 minutes and every 30 minutes (± 5 minutes) after investigational product administration for a minimum of 2 hours (± 5 minutes) or until stable, whichever is later

20) Assess for AEs and SAEs

21) Update concomitant medications

22) Dispense fluticasone/salmeterol or budesonide/formoterol

Day 43 ± 2: Fourth Dose

Visit 6

1) Perform physical examination including weight and neurological examination
2) Collect urine for pregnancy test; ensure result is negative (for females of childbearing potential only)
3) Measure asthma exacerbations
4) Review home peak flow, use of rescue medications, and asthma symptom scores
5) Review ACQ
6) Assess healthcare utilization
7) Review Work Productivity and Activity Impairment Questionnaire
8) Assess for AEs and SAEs
9) Assess injection sites
10) Update concomitant medications
11) Take vital signs before administration of investigational product
12) Administer investigational product
13) Take vital signs within 5 minutes and every 30 minutes (± 5 minutes) after investigational product administration for a minimum of 1 hour (± 5 minutes) or until stable, whichever is later
14) Assess for AEs and SAEs
15) Update concomitant medications

Day 57 ± 2: Fifth Dose

Visit 7

Same as Day 29. except that vital signs will be taken within 5 minutes and every 30 minutes (± 5 minutes) after investigational product administration for a minimum of 1 hour (instead of 2 hours as on Day 29) (±5 minutes) or until stable, whichever is later)

Day 71 ± 2: Sixth Dose

Visit 8

Same as Day 43.

Day 85 ± 2: Seventh Dose

Visit 9

Same as Day 57.

Day 92 ± 2: End of Steroid-stable Phase

Visit 10

1) Spirometry
2) Perform physical examination including weight and neurological examination
3) Take vital signs
4) Perform ECG
5) Collect blood:
   - Whole blood for RNA analysis
6) Collect sputum (at selected sites)
7) Measure asthma exacerbations
8) Review home peak flow, use of rescue medications, and asthma symptom scores
9) Review ACQ
10) Assess healthcare utilization
11) Review Work Productivity and Activity Impairment Questionnaire
12) Assess for AEs and SAEs
13) Assess injection sites
14) Update concomitant medications
15) Dispense fluticasone/salmeterol or budesonide/formoterol

Day 99 ± 2: Eighth Dose

Visit 11

1) Assess mood and behavior using HADS
2) Spirometry
3) Perform physical examination including weight and neurological examination
4) Collect urine for pregnancy test; ensure result is negative (for females of childbearing potential only)
5) Measure asthma exacerbations

6) Review home peak flow, use of rescue medications, and asthma symptom scores
7) Review ACQ
8) Assess healthcare utilization
9) Review Work Productivity and Activity Impairment Questionnaire
10) Assess for AEs and SAEs
11) Assess injection sites
12) Update concomitant medications
13) Take vital signs before administration of investigational product
14) Administer investigational product
15) Take vital signs within 5 minutes and every 30 minutes (± 5 minutes) after investigational product administration for a minimum of 1 hour (± 5 minutes) or until stable, whichever is later
16) Assess for AEs and SAEs
17) Update concomitant medications

Day 113 ± 2: Ninth Dose

Visit 12

1) Spirometry
2) Perform physical examination including weight and neurological examination
3) Collect blood:
   - Serum chemistry
   - Hematology
4) Collect urine for urinalysis
5) Collect urine for pregnancy test; ensure result is negative (for females of childbearing potential only)
6) Measure asthma exacerbations
7) Review home peak flow, use of rescue medications, and asthma symptom scores
8) Review ACQ
9) Review AQLQ(S)
10) Review Patient Global Impression of Severity
11) Assess healthcare utilization
12) Review Work Productivity and Activity Impairment Questionnaire

13) Assess for AEs and SAEs
14) Assess injection sites
15) Update concomitant medications
16) Take vital signs before administration of investigational product
17) Administer investigational product
18) Take vital signs within 5 minutes and every 30 minutes (± 5 minutes) after investigational product administration for a minimum of 1 hour (± 5 minutes) or until stable, whichever is later
19) Assess for AEs and SAEs
20) Update concomitant medications

Day 127 ± 2: Tenth Dose

Visit 13

1) Assess mood and behavior using HADS
2) Spirometry
3) Perform physical examination including weight and neurological examination
4) Collect blood:
   - MEDI-528 serum concentration
   - Anti-MEDI-528 antibodies
5) Collect urine for pregnancy test; ensure result is negative (for females of childbearing potential only)
6) Measure asthma exacerbations
7) Review home peak flow, use of rescue medications, and asthma symptom scores
8) Review ACQ
9) Assess healthcare utilization
10) Review Work Productivity and Activity Impairment Questionnaire
11) Assess for AEs and SAEs
12) Assess injection sites
13) Update concomitant medications
14) Dispense fluticasone/salmeterol or budesonide/formoterol
15) Take vital signs before administration of investigational product
16) Administer investigational product

17) Take vital signs within 5 minutes and at least every 30 minutes (± 5 minutes) after investigational product administration for a minimum of 1 hour (± 5 minutes) or until stable, whichever is later

18) Assess for AEs and SAEs

19) Update concomitant medications

Day 141 ± 2: Eleventh Dose

Visit 14

1) Spirometry

2) Perform physical examination including weight and neurological examination

3) Collect urine for pregnancy test; ensure result is negative (for females of childbearing potential only)

4) Measure asthma exacerbations

5) Review home peak flow, use of rescue medications, and asthma symptom scores

6) Review ACQ

7) Review AQLQ(S)

8) Review Patient Global Impression of Severity

9) Assess healthcare utilization

10) Review Work Productivity and Activity Impairment Questionnaire

11) Assess for AEs and SAEs

12) Assess injection sites

13) Update concomitant medications

14) Take vital signs before administration of investigational product

15) Administer investigational product

16) Take vital signs within 5 minutes and at least every 30 minutes (± 5 minutes) after investigational product administration for a minimum of 1 hour (± 5 minutes) or until stable, whichever is later

17) Assess for AEs and SAEs

18) Update concomitant medications

Day 155 ± 2: Twelfth Dose

Visit 15

1) Assess mood and behavior using HADS

2) Spirometry
3) Perform physical examination including weight and neurological examination
4) Collect urine for pregnancy test; ensure result is negative (for females of childbearing potential only)
5) Measure asthma exacerbations
6) Review home peak flow, use of rescue medications, and asthma symptom scores
7) Review ACQ
8) Assess healthcare utilization
9) Review Work Productivity and Activity Impairment Questionnaire
10) Assess for AEs and SAEs
11) Assess injection sites
12) Update concomitant medications
13) Take vital signs before administration of investigational product
14) Administer investigational product
15) Take vital signs within 5 minutes and at least every 30 minutes (± 5 minutes) after investigational product administration for a minimum of 1 hour (± 5 minutes) or until stable, whichever is later
16) Assess for AEs and SAEs
17) Update concomitant medications

Day 169 ± 2: Thirteenth Dose

Visit 16

1) Spirometry
2) Perform physical examination including weight and neurological examination
3) Collect blood:
    - Serum chemistry (including amylase and lipase)
    - Troponin
    - Hematology
    - MEDI-528 serum concentration
    - Anti-MEDI-528 antibodies
    - IgE-FEIA antibody test
4) Collect urine for urinalysis

5) Collect urine for pregnancy test; ensure result is negative (for females of childbearing potential only)
6) Measure asthma exacerbations
7) Review home peak flow, use of rescue medications, and asthma symptom scores
8) Review ACQ
9) Assess healthcare utilization
10) Review Work Productivity and Activity Impairment Questionnaire
11) Assess for AEs and SAEs
12) Assess injection sites
13) Update concomitant medications
14) Take vital signs before administration of investigational product
15) Administer investigational product
16) Take vital signs within 5 minutes and at least every 30 minutes (± 5 minutes) after investigational product administration for a minimum of 1 hour (± 5 minutes) or until stable, whichever is later
17) Assess for AEs and SAEs
18) Update concomitant medications

Day 176 ± 2: End of Steroid-reduction Phase

Visit 17

1) Assess mood and behavior using HADS
2) Spirometry
3) Perform physical examination including weight and neurological examination
4) Take vital signs
5) Perform ECG
6) Collect blood:
    - MEDI-528 serum concentration
    - Anti-MEDI-528 antibodies
    - Whole blood for RNA analysis
7) Collect sputum (at selected sites)
8) Measure asthma exacerbations
9) Review home peak flow, use of rescue medications, and asthma symptom scores

10) Review ACQ
11) Review AQLQ(S)
12) Review Patient Global Impression of Severity
13) Assess healthcare utilization
14) Review Work Productivity and Activity Impairment Questionnaire
15) Assess injection sites
16) Assess for AEs and SAEs
17) Update concomitant medications

5.2.3 Follow-up Period

Day 204 ± 7: First Follow-up Visit

Visit 18

1) Spirometry
2) Perform physical examination including weight and neurological examination
3) Take vital signs
4) Collect blood:
   - MEDI-528 serum concentration
   - Anti-MEDI-528 antibodies
5) Assess for AEs and SAEs
6) Update concomitant medications
7) Dispense fluticasone/salmeterol or budesonide/formoterol

Day 232 ± 7: Second Follow-up Visit

Visit 19

1) Perform physical examination including weight and neurological examination
2) Take vital signs
3) Collect blood:
   - MEDI-528 serum concentration
4) Assess for AEs and SAEs
5) Update concomitant medications

6) Dispense fluticasone/salmeterol or budesonide/formoterol

Day 260 ± 7: Third Follow-up Visit

Visit 20

1) Spirometry
2) Perform physical examination including weight and neurological examination
3) Take vital signs
4) Perform ECG
5) Collect blood:
   - Serum chemistry
   - Hematology
   - MEDI-528 serum concentration
   - Anti-MEDI-528 antibodies
6) Collect urine for urinalysis
7) Collect urine for pregnancy test (for females of childbearing potential only)
8) Assess for AEs and SAEs
9) Update concomitant medications
10) Dispense fluticasone/salmeterol or budesonide/formoterol

Day 288 ± 7: Fourth Follow-up Visit

Visit 21

Same as Day 232.

5.2.4 Day 323 ± 7: End of Study Visit or Early Discontinuation Visit

Visit 22

These evaluations will be performed on Day 323 (End of Study) or when a subject discontinues the study prematurely, unless the evaluation was performed within 2 weeks of the discontinuation visit.

1) Spirometry
2) Perform physical examination including weight and neurological examination

3) Take vital signs

4) Perform ECG

5) Collect blood:

- Serum chemistry (including amylase and lipase)
- Troponin
- Hematology
- MEDI-528 serum concentration
- Anti-MEDI-528 antibodies
- IgE-FEIA antibody test

6) Collect urine for urinalysis

7) Collect urine for pregnancy test (for females of childbearing potential only)

8) Assess for AEs and SAEs

9) Update concomitant medications

5.3 Description of Study Procedures

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

5.3.1 Mood and Behavior Assessment

Mood and behavior will be assessed at the study site using The Hospital Anxiety and Depression Scale (HADS) and the Columbia-Suicide Severity Rating Scale (C-SSRS) as specified in the study schedule. It is preferred that the HADS and C-SSRS be performed before other study assessments.

Management of subjects with clinically significant anxiety, depression, and/or suicide ideation/behavior will follow the algorithm presented in Appendix 1. If a subject exhibits a clinically significant change in anxiety as assessed by the HADS, then the HADS will be repeated at the next study visit. If a subject exhibits a clinically significant change in depression as assessed by the HADS, the C-SSRS will also be performed at the same visit and the HADS will be repeated at the next study visit.

In the event that the subject endorses suicidal ideation without intent to act as assessed by the C-SSRS, the subject will be referred for formal psychiatric evaluation but can continue in the

study. In the event that the subject exhibits suicidal ideation with intent to act without specific plan or with specific plan and intent, the subject will be withdrawn from the study and referred for formal psychiatric evaluation (and sent to the emergency department if necessary).

5.3.1.1 The Hospital Anxiety and Depression Scale

The HADS is a 14-item questionnaire measuring the presence over the past week of anxiety and depression (Appendix 7). The questionnaire comprises 2 separate domains (anxiety and depression) on a 4 point Likert scale from 0 to 3 (Zigmond et al, 1983). The final score for each domain is the sum of the 7 items such that the final scores for depression and anxiety range from 0 to 21. A score < 8 is normal, 8 to 10 borderline anxiety or depression, 11 to 21 clinically significant anxiety or depression. In addition, a change ≥ 4 points (from Day 1) outside of the normal range for either domain is deemed clinically significant. A change ≥ 4 points (from Day 1) outside of the normal range on the depression scale will result in the administration of the C-SSRS at the same visit (see Appendix 1).

5.3.1.2 The Columbia Suicide Severity Rating Scale

The C-SSRS is a questionnaire that provides for the identification, quantification and standardized assessment of the occurrences and severity of suicidal ideation and behavior (Appendix 8; Baseline and Follow-up). Responses will be classified as follows: 1) suicidal events (completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, and suicidal ideation); 2) non-suicidal events (self-injurious behavior, no suicidal intent and other, no deliberate self-harm); and 3) indeterminate or potentially suicidal events (self injurious behavior, suicidal intent unknown). The C-SSRS must be administered by someone who has received training on the administration of the C-SSRS (eg, investigator or designated site personnel). The C-SSRS should be completed as needed if there are any significant changes noted in the subject's depressive symptoms.

5.3.2 Medical History and Physical Examination

5.3.2.1 Medical and Asthma History

Complete medical history will include history and current medical conditions, past or present cardiovascular disorders, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine,

lymphatic, hematologic, immunologic, dermatological, psychiatric, behavioral/mood, genitourinary, drug and surgical history or any other diseases or disorders.

The asthma history questionnaire, also completed as part of the screening evaluations, includes questions related to the subject's asthma history, duration of asthma, asthma medications, and number of exacerbations/hospitalizations and treatments in the previous 12 months.

5.3.2.2 Physical Examination and Neurological Examination

Physical examinations and neurological examinations will be performed by the investigator or qualified designee. Physical examinations will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, abdominal system, and nervous system. Neurological examinations will include, but are not limited to, assessment of mental status, speech, muscle strength, muscle tone, gait, coordination, sensory, and reflexes. Each clinically significant abnormal finding will be recorded in the electronic case report form.

5.3.3 Vital Signs

All measurements of blood pressure and heart rate will be taken after the subject has been sitting for 5 minutes. Vital signs (blood pressure, pulse, temperature, pulse rate, and respiration rate) will be obtained at every visit. On treatment days vital signs will be taken before and within 5 minutes post investigational product administration every 30 minutes (± 5 minutes) for a minimum of 2 hours (± 5 minutes) or until stable, whichever is later for the first 3 administration visits (ie, Day 1, 15 and 29). During subsequent administrations, vital signs will be obtained before and within 5 minutes and every 30 minutes (± 5 minutes) after investigational product administration for a minimum of 1 hour (± 5 minutes) or until stable, whichever is later. ("Time of dose" is considered the time when the first injection is given.)

5.3.4 Chest X-ray

All subjects will have a chest x-ray during screening or must provide documentation of a chest x-ray within 12 months prior to randomization. The chest x-ray must be normal for inclusion in the study. Signs of hyperinflation are allowed.

5.3.5 Electrocardiogram

Computerized 12-lead ECG recordings will be obtained, after the subject has been supine for 10 minutes. Each lead will be recorded for at least 3 to 5 beats at a speed of 25 mm/sec paper speed and 10 mm/mV amplitude. Heart rate, P, PR, QRS, QT and QTc intervals (msec) will be recorded from the 12-lead ECG.

5.3.6 Concomitant Medications

All concomitant medications, including vitamins and supplements, will be recorded on the collection instrument provided from Screening through Day 176.

5.3.7 Clinical Laboratory Tests

Clinical laboratory safety tests for the screening and the treatment periods will be performed in a licensed central clinical laboratory. Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours). Urine pregnancy tests (for females of childbearing potential only) on Day 1 prior to dosing and during the treatment period will be performed in the clinic using a licensed test (dipstick).

The following clinical laboratory tests will be performed (see Table 5.2-1 and Table 5.2-2 for the schedule of tests):

Serum Chemistry

- Calcium
- Chloride
- Magnesium
- Potassium
- Sodium
- Aspartate transaminase (AST)
- Alanine transaminase (ALT)
- Alkaline phosphatase (ALP)
- Gamma glutamyl transferase (GGT)
- Lactic dehydrogenase (LDH)
- Blood urea nitrogen (BUN)
- Uric acid
- Creatinine
- Total bilirubin
- Free glucose
- Albumin
- Total protein
- Free triglycerides
- Free cholesterol
- Amylase (only on Days 1, 169, and 323/Discontinuation)
- Lipase (only on Days 1, 169, and 323/Discontinuation
- Troponin (only on Days 1, 169, and 323/Discontinuation

Hematology

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hematocrit
- Hemoglobin
- Platelet count
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Blood
- Bilirubin
- Microscopy including WBC/high power field (HPF), RBC/HPF

Pregnancy Test (females of childbearing potential only)

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

Other Safety Tests

- Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody
- HIV-1 and HIV-2 antibody
- Safety biomarkers (as instructed per Section 5.3.10)

5.3.8 Pharmacokinetic Evaluation and Methods

Blood samples for MEDI-528 concentration determination will be collected at selected study visits. MEDI-528 serum concentrations will be measured by enzyme-linked immunosorbent assay (ELISA) or electrochemiluminescent assay (ECLA).

5.3.9 Immunogenicity Evaluation and Methods

The presence of anti-MEDI-528 antibodies will be evaluated in serum. Anti-MEDI-528 antibody detection will be measured by ELISA or ECLA. A sample will be collected prior to investigational product administration on Day 1. Additional samples will be collected according to the study schedule.

5.3.10 Safety Biomarker Evaluation and Methods

Serum samples will be collected for baseline assessment of safety biomarkers on Day 1. In addition, if a moderate to severe (as defined in Section 6.2.1) hypersensitivity reaction occurs during or within a 24-hour period after administration of investigational agent, whole blood for assessment of safety biomarkers will be collected as soon as possible after the event, at 60 minutes after the event, and at discharge. Safety biomarkers include serum levels of mast cell tryptase, cytokines/chemokines, and anti-drug antibodies of IgE isotype.

5.3.11 Disease Evaluation and Methods

5.3.11.1 Asthma Control Questionnaire

The 6-item ACQ is a patient-reported questionnaire assessing asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing) and daily rescue bronchodilator use (Appendix 4). The ACQ will be completed weekly at home in the electronic Patient-reported Outcome (ePRO) device. Sites will be asked to ensure subject compliance with the ACQ at each visit from Day -28 to Day 176. Subjects are asked to recall how their asthma has been during the previous week by responding to 5 symptom and bronchodilator use questions (Juniper et al, 1999). Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.76 and < 1.5 indicate partly controlled asthma, and a score ≥ 1.5 indicates uncontrolled asthma (Juniper et al, 2006). Individual changes of at least 0.5 are considered to be clinically meaningful (Juniper et al, 2005).

5.3.11.2 Asthma Quality of Life Questionnaire (Standardized Version)

The AQLQ(S) is a 32-item questionnaire that measures the health related quality of life experienced by asthma patients (Juniper et al, 1999) and will be completed at home in the ePRO device (Appendix 5). Sites will be asked to ensure subject compliance with the AQLQ at select visits (Days 1, 29, 57, 85, 113, 141, and 176). The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli). Subjects are asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The 4 individual domain scores (symptoms, activity limitations, emotional function, and

environmental stimuli) are the means of the responses to the questions in each of the domains. Individual improvement in both the overall score and individual domain scores of 0.5 has been identified as the minimally important difference, with score changes > 1.5 identified to be large meaningful differences (Juniper et al, 1994).

5.3.11.3 Patient Global Impression of Severity

Patient Global Impression of Severity (Appendix 6) is a single-item question about the subject's asthma status and will be completed at home in the ePRO device. Sites will be asked to ensure subject compliance with the Patient Global Impression of Severity at select visits (Days 1, 29, 57, 85, 113, 141, and 176). For this assessment, the subject responds to the single item question about the overall feelings about their asthma during the past week using a 5-point scale with responses ranging from 1 ("The best I've ever felt") to 5 ("The worst I've ever felt").

5.3.11.4 Healthcare Utilization

Healthcare resource use will be summarized from information on asthma-related medical provider encounters and medications. Absolute number and proportion of healthcare resource utilization by resource type will be reported.

5.3.11.5 Work Productivity and Activity Impairment Questionnaire

The Work Productivity and Activity Impairment questionnaire will be used to measure self-reported productivity loss (Appendix 9) and will be completed at home on the ePRO device. Sites will be asked to ensure subject compliance with the Work Productivity and Activity Impairment Questionnaire at each visit from Day -28 to Day 176. It consists of questions about absence from work due to asthma problems, hours actually worked, the reduction in productivity at work and about the reduction in productivity while performing regular activities. The questionnaire relates to the previous 7 days.

5.3.11.6 Asthma Symptom Score

Daily Asthma Symptom Scores will be assessed by the subject every morning from screening through Day 176 and recorded at home in the ePRO device. Subjects are asked to recall over the past 24 hours their experience with daytime symptoms (0-4 scale), night-time symptoms (0-4 scale), and morning scores (0-1 scale). Sites will be asked to ensure subject compliance with the Daily Asthma Symptom Scores at each visit.

5.3.11.7 Reversibility of FEV_1

Reversibility of FEV_1 will be evaluated as described by Miller (Miller et al, 2005). To determine whether there is any evidence of reversible airflow limitation, the subject should undergo baseline function testing when not taking any drugs prior to the test. Short-acting inhaled drugs (eg, β2-agonists albuterol/salbutamol or the anticholinergic agent ipratropium bromide) should not be used within 4 hours of testing.

Long-acting β2-agonist bronchodilators (eg, salmeterol or formoterol) and oral therapy with aminophylline or slow-release β-agonists should be stopped for 12 hours prior to the test.

Smoking should be avoided for ≥ 1 hour prior to testing and throughout the duration of the test procedure. The following steps are undertaken: 1) The subject has 3 acceptable tests of FEV_1, FVC and PEF recorded as described by Miller (Miller et al, 2005); 2) The drug is administered in the dose and by the method indicated for the test. For example, after a gentle and incomplete expiration, a dose of 100 µg of albuterol/salbutamol is inhaled in one breath to total lung capacity (TLC) from a valved spacer device. The breath is then held for 5 to 10 seconds before the subject exhales. Four to 6 separate doses (total dose 400-600 µg) are delivered at approximately 30-second intervals. This dose ensures that the response is high on the albuterol/salbutamol dose-response curve. A lower dose can be used if there is concern about any effect on the subject's heart rate or tremor. Other drugs can also be used in addition to albuterol/salbutamol. For the anticholinergic agent ipratropium bromide, each dose is 40 µg (total dose 160-240 µg). Three additional acceptable tests are recorded for 10 minutes and up to 15 minutes later for short-acting β2-agonists, and 30 minutes later for short-acting anticholinergic agents.

5.3.11.8 Methacholine Inhalation Challenge Testing

The methacholine inhalation challenge must be completed in the morning ± 1 hour at each assessment, if applicable. Direct challenges using methacholine cause airflow obstruction by acting directly on airway smooth muscle to reduce FEV_1. Methacholine inhalation challenge testing will be performed using either of 2 ATS guideline recommended methodologies: the 2-minute tidal breathing method or the 5 breath dosimeter method (American Thoracic Society, 2000). The same method should be used on individual subjects for both entry and exit methacholine challenges. At each stage the maximum FEV_1 will determine the best effort; the highest FVC and peak flow will also be recorded even if they are obtained in different efforts from the maximum FEV_1. Only 2 efforts are required at each stage if these

efforts are considered by the investigator or qualified designee to be representative of the subject's ability to perform spirometry at that stage. In general, no more than 3 efforts should be performed at each stage in order to conserve the subject's ability to perform spirometry for the duration of the test.

Contraindications for methacholine challenge testing include:

- FEV_1 < 1.5 L or < 60% of predicted
- A heart attack or stroke in the previous 3 months
- A known aortic aneurysm
- Uncontrolled hypertension (systolic >200 mm Hg or diastolic >100 mm Hg)
- Current use of anticholinesterase medication for myasthenia gravis
- A respiratory infection in the previous 6 weeks
- Subject is having an acute asthma attack on day of study
- An oral corticosteroid burst in the previous 30 days
- Prohibited medication or food as described in Table 5.3.7.3-1

Subjects who are not eligible for methacholine challenge during the screening/run-in period or at the end of the study will not be rescheduled. Adverse events or SAEs resulting from methacholine inhalation challenge testing should be reported.

Table 5.3.7.3-1 Prohibited Medication or Food and Minimum Time Intervals Prior to Methacholine Inhalation Challenge Testing

Concomitant Medication or Food	Minimum Time Interval from Last Medication Dose or Food to Methacholine Challenge Testing
Inhaled bronchodilators	
Short-acting β2 agonists (albuterol/salbutamol, levalbuterol, etc.)	6 hours
Long-acting β2 agonists (salmeterol, formoterol)	12 hours
Ipratropium bromide	8 hours
Tiotropium bromide	24 hours
Cromolyn	8 hours
Nedocromil	24 hours
Oral bronchodilator	
Standard β2 agonist tablets	12 hours
Long-acting β2 agonist tablets	24 hours

Table 5.3.7.3-1 Prohibited Medication or Food and Minimum Time Intervals Prior to Methacholine Inhalation Challenge Testing

Concomitant Medication or Food	Minimum Time Interval from Last Medication Dose or Food to Methacholine Challenge Testing
Theophylline	24 hours
Other medications	
Leukotriene modifiers	24 hours
Foods	
All caffeinated beverages (eg, coffee, tea, cola drinks, Mellow Yellow, Mountain Dew), chocolate (caffeinated foods), alcohol	12 hours

The fall in FEV_1 is calculated as a percentage of the best FEV_1 determined at the saline stage. Subjects with a positive test or who are symptomatic should receive 2-4 puffs of albuterol/salbutamol and be observed until their FEV_1 returns to at least 90% of the baseline value. Subjects who have a decrease in FEV_1 of > 50% should be rescued with albuterol/salbutamol and followed closely. If the FEV_1 does not return to at least 90% of baseline (pre-diluent) value, the subject should not be discharged from the clinic without the approval of the investigator or qualified designee.

The PC_{20} methacholine will be calculated as outlined in the ATS guideline paper (ATS, 1999). The cutoff for a positive test will be a PC_{20} of ≤ 8 mg/mL.

5.3.11.9 Office Spirometry

Spirometry at study sites will be performed by the investigator or qualified designee according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al, 2005). Spirometry testing must be performed between 6:00 AM and 11:30 AM. All post-screening spirometry testing must be completed within 1 hour of the screening spirometry. For example, if the screening spirometry is at 10:00 AM, then all subsequent spirometry testing needs to be completed between 9:00 AM and 11:00 AM.

Restrictions prior to spirometry are listed in Table 5.3.11.9-1.

Table 5.3.11.9-1 Restrictions Prior to Office Spirometry

Drug	Time Limit
Smoking	1 hour prior

Table 5.3.11.9-1 Restrictions Prior to Office Spirometry

Drug	Time Limit
Short-acting β2-agonist	4 hours prior
Short-acting muscarinic antagonist	8 hours prior
Strenuous exercise	12 hours prior
Long-acting β2-agonist	12 hours prior
Slow-release β2-agonist	12 hours prior
Oral aminophylline	12 hours prior
Caffeinated food products	12 hours prior
Inhaled disodium cromoglycate	12 hours prior
Inhaled nedocromil sodium	12 hours prior
Leukotriene modifiers	24 hours prior
Long-acting muscarinic antagonist	2 weeks prior

Subjects should be sitting during spirometry testing; however, if the subject is unable to sit, then standing is acceptable. Spirometry testing should be completed in the same manner (ie, sitting or standing) at every study visit.

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each office spirometry session and the two 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 two best efforts will be used for the analysis. The absolute measurement (for FEV_1 and FVC), and the percentage of predicted normal value (Hankinson et al, 1999) will be recorded. 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.

5.3.11.10 Asthma exacerbations

For the purpose of this study, an asthma exacerbation (relapse or de novo) is defined as a progressive increase of asthma symptoms (cough, wheeze, chest tightness, and/or shortness of breath) AND a reduction of ≥ 20% in PEF or FEV_1 from baseline or best previously measured value prior to the current event that does not resolve after the initiation of rescue

medications; and results in a prescription for/or administration of systemic corticosteroid burst therapy by the investigator or health care provider (see Appendix 3).

An exacerbation event will be considered resolved when the subject's asthma symptoms diminish and PEF or FEV_1 return to > 80% of baseline for ≥ 7 days after completion of systemic corticosteroid burst therapy.

Asthma exacerbation severity will be classified as follows:

- Moderate: Worsening symptoms requiring systemic corticosteroids.
- Severe: Worsening symptoms requiring systemic corticosteroids and hospital admission.

5.3.11.11 Home Peak Flow Testing

Home peak flow testing for FEV_1 and PEF will be performed once daily from the screening visit through Day 176. Subjects should perform peak flow testing every morning while sitting or standing, but in the same position at every testing. Peak flow meters for home and instructions for data recording will be provided to each enrolled subject at screening.

5.3.11.12 Use of Rescue Medication

Use of rescue medication will be collected daily by the subject from screening through Day 176 and recorded at home in the ePRO device. Information regarding the use of concomitant controller medication use will be collected during the scheduled study visits.

5.3.11.13 Other Disease Evaluations

Additional whole blood and sputum samples (at selected sites) will be collected on Days 1, 92 and 176. Whole blood samples (for both PAXgene tube collection = 2×2.5 mL and serum 2×5 mL) collected from subjects in each treatment group will be used for gene array and proteomics, and also for tryptase measurements to assess if constitutive tryptase levels are reduced following prolonged IL-9 inhibition. Induced sputum will be used for proteomics transcription analyses. These analyses will include, but are not limited to, mucin protein and transcript levels and tryptase levels to determine effects of anti-IL-9 inhibition on lung resident mast cell activation/numbers.

Serial sputum induction must be separated in time by at least 7 days. Sputum will be induced and analyzed in subjects as described by Pizzichini (Pizzichini et al, 1996). Subjects should not use the following prior to sputum induction:

- Short-acting β2-agonists for at least 6 hours
- LABAs for at least 12 hours
- Leukotriene modifiers for at least 24 hours prior to the visit.

Subjects will receive 2 puffs of albuterol/salbutamol MDI, and then spirometry will be performed 15 to 20 minutes later. If the FEV_1 is < 60%, an additional 2 puffs of albuterol/salbutamol will be administered and repeat spirometry will be performed 15 to 20 minutes later. If the FEV_1 is:

- < 50%, then the sputum induction will need to be rescheduled. The site will need to call MedImmune to determine when the subject should return.
- If the FEV_1 is between 50% and 60%, sputum induction may proceed at the investigator's discretion.
- If the FEV_1 is ≥ 60%, then sputum induction may proceed.

The subject will then sequentially inhale 3%, 4%, and 5% saline for 7 minutes each. Scheduled FEV_1 measurements will be obtained prior to each saline nebulization and halfway through (approximately 3 1/2 minutes) each saline treatment. The induction will be stopped when an adequate sample is obtained or if the subject's FEV_1 drops ≥ 20% from baseline. Samples will be aspirated in dithiothreitol (DTT) and Dulbecco's phosphate buffered saline (PBS).

Specific procedures for collection, processing, storage, and shipping are provided in the laboratory manual.

5.3.12 Estimate of Volume of Blood to Be Collected

The estimated volume of blood to be collected from each subject at each visit from screening through the Discontinuation Visit/End of Study (Day 323) and the total volume of blood to be collected over the entire study are presented in Table 5.3.12-1.

Table 5.3.12-1 Estimated Volume of Blood to be Collected per Visit

Visit	Estimated Blood Volume	
	Milliliters	**Teaspoons**
Day -28	26.0	5.2
Day -14	0	0
Day 1	30.5	6.1
Day 15	7.0	1.4
Day 29	17.5	3.5
Day 43	0	0
Day 57	17.5	3.5
Day 71	0	0
Day 85	17.5	3.5
Day 92	9.0	1.8
Day 99	0	0
Day 113	10.5	2.1
Day 127	7.0	1.4
Day 141	0	0
Day 155	0	0
Day 169	25.0	5
Day 176	16.0	3.2
Day 204	11.0	2.2
Day 232	7.0	1.4
Day 260	21.5	4.3
Day 288	7.0	1.4
Day 323/Discontinuation	29.0	5.8
Overall Total	**259**	**51.8**

6 Assessment of Safety

6.1 Safety Parameters

6.1.1 Adverse Events

The ICH Guideline for Good Clinical Practice E6(R1) defines an adverse event (AE) as:

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

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition.

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

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

6.1.2 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 may have led to death.

- Requires inpatient hospitalization or prolongation of existing hospitalization

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

- Results in persistent or significant disability/incapacity

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

- Is a congenital anomaly/birth defect in offspring of the subject

- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

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

6.2 Assessment and Recording of Safety Parameters

6.2.1 Assessment of Severity

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

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

Grade 5 The termination of life as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.1.2. A Grade 3 or Grade 4 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

6.2.2 Assessment of Relationship

An event is considered "product-related" for the purposes of regulatory reporting if the investigator, the MedImmune medical monitor, or the MedImmune Patient Safety Physician assesses the event as possibly, probably, or definitely related to the 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 event is treated as product-related for the purposes of reporting to regulatory authorities.

An event may be deemed to be not related to the product for purposes of regulatory reporting only if the investigator, MedImmune medical monitor, and MedImmune Patient Safety Physician, if applicable, agree that the event 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 event 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.

6.2.3 Recording of Adverse Events

Adverse events will be recorded on the CRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification of the sponsor. See Section 6.1.2 for the definition of SAEs, and Section 6.2.1 and Section 6.2.2 for guidelines for assessment of severity and relationship, respectively. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form (Section 6.2.4).

6.2.4 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. Serious adverse events will be assessed

by the investigator for severity, relationship to the investigational product, and possible etiologies. See Section 6.1.2 for the definition of SAEs, and Section 6.2.1 and Section 6.2.2 regarding guidelines for assessment of severity and relationship, respectively.

For SAEs that occur prior to the administration of investigational product (nontreatment-emergent SAEs), an assessment of protocol relatedness must be made by the investigator. A protocol-related SAE may occur as a result of a procedure or intervention required during the screening process (eg, blood collection, washout of an existing medication) prior to the initial administration of investigational product. The following guidelines should be used by investigators to assess the relationship of nontreatment-emergent SAEs:

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

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

6.3 Reporting Requirements for Safety Parameters

6.3.1 Study Reporting Period for Adverse Events

The reporting period for AEs is the period immediately following the time that written informed consent is obtained through Day 323. Any AE that starts within the reporting period will be followed to resolution, even if the date extends beyond the reporting period, up to the end of the clinical study (Day 323). New (nonserious) AEs that start after the reporting period will not be collected.

6.3.2 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 Day 323. After submitting an initial SAE report for a subject (to MedImmune Patient Safety), the investigator is required to follow the subject proactively and provide further information on the subject's condition to MedImmune Patient Safety.

The investigator is responsible for following all SAEs until resolution, even if this extends beyond the study reporting period, or until the subject returns to baseline status or the condition has stabilized 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 must be reported to MedImmune Patient Safety.

6.3.2.1 Notifying the Sponsor of Serious Adverse Events

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

MedImmune contact information:

Patient Safety
MedImmune
[redacted]
Fax: [redacted]

As sponsor of the study, MedImmune is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH Guidelines and/or local regulatory requirements. 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 SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying MedImmune Patient Safety of an SAE. When additional information becomes available, submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Patient Safety within 24 hours of learning of the new information.

6.3.2.2 Notifying the 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 IRB/IEC. The IRB/IEC must be informed in a timely manner by the investigator of SAEs occurring at their site during the study. Investigators must also submit safety information provided by MedImmune to the IRB/IEC as detailed in Section 10.1 and Section 10.2.

6.3.3 Other Events Requiring Immediate Reporting

6.3.3.1 Pregnancy and Overdose

The following events are not necessarily considered to be AEs but are required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the Fax Notification Form (see Section 6.3.2.1 for contact information):

1) Pregnancy (including the intention to become pregnant)
2) Investigational product overdose (whether or not the overdose is associated with an AE or SAE)

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

6.3.3.2 Other Protocol-specific Events

The following events are considered immediately reportable events and must be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient using the Fax Notification Form (see Section 6.3.2.1 for contact information):

1) Any withdrawal of consent during the study
2) Any event resulting in discontinuation of investigational product
3) Anaphylactic reaction (see Appendix 2)
4) Change from baseline of ≥ 4 points on the HADS depression score.

6.4 Safety Management During the Study

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

The MedImmune Safety Monitoring Committee (SMC) will independently review cumulative safety surveillance data on a regular basis and make recommendations regarding further conduct of the study. The SMC is composed of internal MedImmune employees and physicians who are not employees of MedImmune. A quorum is defined by an assembly of 60 percent of the internal voting members and at least two external voting members. The MedImmune SMC will review safety data at other time points in response to AEs felt to be medically significant by the medical monitor. The MedImmune 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.

6.4.1 Interruption or Permanent 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:

1) Withdrawal of consent
2) Pregnancy
3) Event which, in the opinion of the investigator, contraindicates further dosing such as illnesses or complications
4) Anaphylactic reaction to the investigational product (see Appendix 2)
5) Suicidal ideation with intent to act or suicidal attempt

Subjects who are permanently discontinued from receiving investigational product will be followed for safety for approximately 5 half-lives of the investigational product, including the collection of any protocol-specified blood, urine, or nasal specimens, unless consent is withdrawn.

6.4.2 Study Stopping Criteria

If any of the following occur, administration of investigational product will be stopped and no additional 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) Anaphylactic reaction to investigational product in any subject
3) The occurrence of immune complex disease
4) Events that, in the opinion of the medical monitor and SMC contraindicate further dosing of additional subjects.

If any 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, Patient Safety Physician, and/or the MedImmune SMC, to determine whether dosing and study randomization should be resumed, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the MedImmune SMC are required for resumption of the study in the event the study is interrupted because of one of the above-listed events. Where applicable, regulatory authorities and IRBs/IECs will be notified of any actions taken with the study.

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

6.4.3 Monitoring of Dose Administration

As with any antibody, allergic 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 trained to recognize and treat anaphylaxis.

7 Statistical Considerations

7.1 General Considerations

Data will be provided in data listings sorted by treatment group and subject number. Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Confidence intervals (CIs) will be 2-sided, unless otherwise stated. Details of endpoint analyses will be described in the statistical analysis plan.

7.2 Analysis Populations

The Intent-to-Treat (ITT) Population includes all subjects who are randomized into the study. Treatment group will be assigned according to the initial randomization, regardless of whether subjects receive any investigational product or receive an investigational product different from that to which they were randomized.

The According-to-Protocol (ATP) Population includes all subjects who receive a minimum number of doses of the investigational product and have no major protocol violations. The number of minimum doses and major protocol violations for the ATP Population will be identified prior to database lock (ie, prior to restricting access to the clinical study database after known data processing activities are complete).

The Safety Population includes all subjects who receive any investigational product and have safety data available. The safety analyses will be presented on an as-treated basis.

The Evaluable Population for PK includes all subjects who receive at least one dose of investigational product and have a sufficient number of serum concentration measurements for computing PK parameters. The Evaluable Population for immunogenicity includes all subjects who receive at least one dose of investigational product.

Detail of each population above and any additional population, if needed, will be described in the Statistical Analysis Plan.

7.3 Endpoints

7.3.1 Primary Endpoint

The primary objective of this study is to evaluate the effect of multiple-dose SC administration of MEDI-528 on asthma control. The primary endpoint analysis will be conducted using the ITT Population. The primary endpoint is the change from baseline in the mean ACQ score at Day 92. For subjects in the ITT Population without an ACQ measurement at Day 92, the latest available measurement prior to Day 92 will be used.

Comparisons between individual MEDI-528 treatment groups (30 mg, 100 mg, or 300 mg) and placebo will be conducted. An analysis of covariance (ANCOVA) model will be tested using a 2-sided test. The model will include the change from baseline in the mean ACQ score at Day 92 as the dependent variable. The model will also include the treatment groups (MEDI-528 treatment groups vs placebo), atopic asthma status, and geographic region (pooled centers) as independent factors. The mean ACQ score at baseline will be included as a covariate in the model. An additional factor may be included in the model to adjust for use of concomitant asthma controller medications.

A repeated measures analysis may also be conducted using a similar model. The change from baseline in the mean ACQ score will be the repeated measures. Note that such repeated measures analyses are exploratory in nature and no conclusions will be drawn with regard to the primary objective of this study. Missing measurements may be imputed for such repeated measures analyses.

7.3.2 Secondary Endpoints

7.3.2.1 Safety

The safety of MEDI-528 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 Day 323. Laboratory measurements will be evaluated as changes from baseline at each collection time point. The results of HADS and C-SSRS will be summarized descriptively.

7.3.2.2 Effect of MEDI-528 on Asthma Exacerbations

The asthma exacerbation rate and severity (hospitalizations) will be compared between the individual MEDI-528 treatment groups and placebo if sufficient data are available. The proportion of subjects that experienced one or more exacerbations during the study will be compared between the MEDI-528 treatment groups and placebo using the Fisher's exact text. The proportion will also be compared between the individual MEDI-528 treatment groups and placebo using the Cochran-Mantel-Haenszel (CMH) test. A stratified comparison will also be conducted using the CMH test with severity level, atopic asthma status, and fluticasone/salmeterol or budesonide/formoterol dose as possible stratification factors. The number of exacerbation-free days will also be summarized.

7.3.2.3 Effect of MEDI-528 on Asthma Control

7.3.2.3.1 Effect of MEDI-528 on ACQ at the Steroid-stable, and Steroid-reduction Phases

Analyses conducted for this secondary endpoint will be similar to those conducted for the primary endpoint. Comparisons between individual MEDI-528 treatment groups (30 mg, 100 mg, or 300 mg) and placebo will be conducted on asthma control at the steroid-stable and steroid-reduction phases separately.

The proportion of subjects achieving ACQ ≤ 0.75 (well-controlled) and the proportion of subjects achieving ACQ of ≤ 1.5 during the study will be compared between the individual and combined MEDI-528 treatment groups and placebo using the Fisher's exact test.

7.3.2.3.2 Effect of MEDI-528 on the Patient Global Impression of Severity

The patient global impression of severity will be summarized using descriptive statistics.

7.3.2.3.3 Effect of MEDI-528 on the Time to First Improvement in Asthma Control

A secondary objective of this study is to evaluate the effect of multiple-dose SC administration of MEDI-528 on the time to first improvement in asthma control using the ACQ through Day 176. Subjects with baseline mean ACQ scores ≥ 1.5 will be randomized. The ACQ scores will be collected according to the schedule in Table 5.2-1 and Table 5.2-2. The endpoint will be the number of days from Day 1 to the post-baseline ACQ measurement time point when a reduction from baseline in the mean ACQ score ≥ 0.5 is first observed.

Subjects who do not meet this ACQ response criterion by the Day 176 assessment will be considered censored at that time point. A stratified log-rank test will be conducted to compare the time to first improvement in asthma control between the combined as well as individual MEDI-528 treatment groups and placebo. Atopic asthma status and fluticasone/salmeterol or budesonide/formoterol dose will be used as the stratification factor. A proportional hazard model may be used to explore the effect of some covariates such as the use of concomitant controller and rescue medication. The median for the time to first improvement in asthma control along with a 2-sided 95% confidence interval may be estimated for individual MEDI-528 treatment groups and placebo by using the Kaplan-Meier method if enough uncensored data are available to compute a median.

7.3.2.3.4 Effect of MEDI-528 on Use of Concomitant Controller, Fluticasone/salmeterol or Budesonide/formoterol, Rescue Medications, and Symptom Scores

The use of concomitant controller, use of fluticasone/salmeterol or budesonide/formoterol, rescue medications, and symptom scores during the 46-week study will be summarized descriptively. For reduction of fluticasone/salmeterol or budesonide/formoterol, the number of subjects with dose reduction (see Section 4.6.2.2) will be reported for each group.

7.3.2.4 Effect of MEDI-528 on Pulmonary Function

The effect of MEDI-528 on pulmonary function as measured by improvements of airflow obstruction (FEV_1 and FVC at the site and PEF and FEV_1 at home) during the study will be assessed. The measurements along with change from baseline in the mean score at various time points will be summarized using descriptive statistics. Two-sample t-test may be used to compare the changes from baselines in the subject's FEV_1 and PEF for the morning between the individual MEDI-528 treatment groups and placebo.

7.3.2.5 Effect of MEDI-528 on Health-related Quality of Life

A secondary objective of this study is to evaluate the effect of MEDI-528 on HRQOL as measured by the AQLQ(S).

The overall and 4 domain scores from the AQLQ(S) responses along with their respective changes from baseline will be summarized using descriptive statistics. Additionally, the proportion of AQLQ(S) responders (subjects with >0.5 improvement from baseline in AQLQ(S) scores) at each visit will be reported.

7.3.2.6 Pharmacokinetics and Immunogenicity of MEDI-528

The PK and IM of MEDI-528 in this subject population will be evaluated. Individual MEDI-528 serum concentrations will be tabulated by treatment group along with descriptive statistics.

The incidence rate of positive serum antibodies to MEDI-528 will be reported by treatment group.

7.3.3 Exploratory Endpoints

Healthcare utilization will be summarized using descriptive statistics.

The effect of MEDI-528 on productivity will be assessed using the Work Productivity and Activity Impairment questionnaire. Data collected using this questionnaire will be summarized using descriptive statistics by treatment groups.

Other exploratory assessments may include, but are not limited to, gene array, proteomics, and mast cell tryptase measurements from whole blood samples and proteomics (both cells and fluid), [redacted]. These data, if available, will be summarized using descriptive statistics by treatment groups.

7.4 Interim Analysis

Two interim analyses are planned for this study.

The first interim analysis will be conducted after all subjects have completed the Day 92 evaluations. The primary endpoint analysis outlined in Section 7.3.1 will constitute the first interim analysis. Since the primary endpoint analysis for which this study is powered will be completed at the first interim analysis, it will not be repeated at the end of the study. As such there is no need for multiplicity adjustment of the Type I error.

The second interim analysis will be conducted after all subjects have completed the Day 176 evaluations. Evaluation of asthma exacerbation will constitute the second interim analysis.

Analyses of safety data available at the time of data cut-off will be presented in the interim analyses. If necessary, analyses of limited secondary endpoints may be included in the

interim analyses. The interim analyses will be described in detail in the SAP. The results of the interim analyses will be communicated with only limited numbers of MedImmune Senior Management personnel, independent of the clinical study team conducting the study and will be identified in the unblinding plan before the interim analysis is performed.

There will be no adjustment for any covariates, multiple comparisons or center (block) effect in this multicenter study. P-values will be provided without multiplicity adjustment.

7.5 Sample Size and Power Calculations

Sample size estimations have been performed for the primary endpoint of change from baseline in the mean ACQ score at Day 92 in adult subjects with uncontrolled, moderate-to-severe, persistent asthma.

It is assumed that the change from baseline in the mean ACQ score at Day 92 will be -0.4 to -0.5 and -0.9 to-1.1 for the placebo and each MEDI-528 treatment group, respectively, with a common standard deviation of 0.8 to 1.0 (Molimard et al, 2005; Giraud et al, 2006). With approximately 60 subjects in each treatment group (a total of 240 subjects), the statistical power for detecting a statistically significant difference in the change from baseline in the mean ACQ score at Day 92 will be between 58% and 99% based on the above assumptions and a 2-sided t-test with Type I error of $\alpha = 0.05$ and 0.10 and a randomization ratio of 1:1:1:1. See Table 7.5-1 for power calculations with different assumptions on standard deviation, alpha and mean ACQ scores for placebo and MEDI-528. Assuming a drop-out rate of about 20% in the study, a total of 320 randomized subjects are expected to provide 240 subjects for the study. The 320 subjects will be randomized at a ratio of 1:1:1:1 to 1 of 4 treatment groups to receive MEDI-528 or placebo every 2 weeks for 24 weeks, with approximately 80 subjects randomized to each treatment group (3 MEDI-528 treatment groups and placebo).

Table 7.5-1 Power Calculations for Different Assumptions with Approximately 60 Subjects in Each Treatment Arm

		Placebo -0.4			Placebo -0.5		
Treatment	**Type I Error**	**SD 0.8**	**SD 0.9**	**SD 1.0**	**SD 0.8**	**SD 0.9**	**SD 1.0**
MEDI-528 -0.9	Alpha 0.05	92	85	77	77	67	58
	Alpha 0.1	96	91	85	85	78	70
MEDI-528 -1.0	Alpha 0.05	98	95	90	92	85	77
	Alpha 0.1	99	97	94	96	91	85
MEDI-528 -1.1	Alpha 0.05	99	98	96	98	95	90
	Alpha 0.1	99	99	98	99	97	94

The above sample size computation is for comparisons between each MEDI-528 treatment group versus placebo. The sample size computation is not adjusted for the stratification based on atopic asthma status and fluticasone/salmeterol or budesonide/formoterol dose, since good estimates for each stratum are unavailable. The aim of stratification is to obtain at least 160 randomized subjects (at least 40 subjects in each treatment group) with atopic asthma in the study and to obtain the same number of subjects in fluticasone/salmeterol 250 µg/50 µg or budesonide/formoterol 160 µg/4.5 µg strata and fluticasone/salmeterol 500 µg/50 µg strata in the placebo group and each MEDI-528 treatment group. The sample size computation was done using the nQuery Advisor® 6.01 statistical software.

Table 7.5-2 and Table 7.5-3 present the probability of observing at least 1 subject with an infrequently occurring AE when assuming a range of potential observed event rates and exact binomial 95% confidence intervals to assess the precision of estimates of the AE rate for MEDI-528.

Table 7.5-2 Expected Number of Subjects with AEs and Probabilities of Observing at Least 1 or 2 Subjects with Adverse Events Given the True Event Rates

N	True Event Rate (%)	Number of Subjects with AEs Expected	Probability of Observing at Least 1 Subject with an AE (%)	Probability of Observing at Least 2 Subjects with AEs (%)
80	1	1	55.2	19.1
80	2	2	80.1	47.7
80	3	2	91.3	69.6
160	1	2	80.0	47.6
160	2	3	96.1	83.2
160	3	5	99.2	95.5
240	1	2	91.0	69.3
240	2	5	99.2	95.4
240	3	7	99.9	99.4

Table 7.5-3 Estimated AE Rates and 95% Exact Binomial Confidence Intervals Given the Number of Subjects with Adverse Events Observed

N	Number of Subjects With AEs Observed	Estimated Event Rate (%)	95% Confidence Interval (%)
80	0	0.0	(0.0, 4.5)
80	1	1.3	(0.0, 6.8)
80	5	6.3	(2.1, 14.0)
160	0	0.0	(0.0, 2.3)
160	1	0.6	(0.0, 3.4)
160	5	3.1	(1.0, 7.1)
240	0	0.0	(0.0, 1.5)
240	1	0.4	(0.0, 2.3)
240	5	2.1	(0.7, 4.8)

8 Direct Access to Source Data and Documents

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.

9 Quality Control and Quality Assurance

9.1 Data Collection

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

Subject demographics and key/essential disease baseline characteristics thought to affect outcome, ie, stratification variables and other prognostic factors, will be collected, as available, for all subjects who provide written informed consent. For subjects who provide informed consent and were not entered/randomized into the study, 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), will also be collected.

9.2 Study Monitoring

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

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

The monitor will visit study facilities at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter. The monitor will assess subject enrollment and informed consent procedures; investigational product storage, dispensing,

administration and accountability; compliance with protocol procedures; completeness and accuracy of data entered onto validated data collection instruments (paper CRF or electronic data screen) against original source documents; and the occurrence of AEs/SAEs. All aspects of the study will be carefully monitored for compliance with the protocol, applicable government regulations, GCP, and the site's standard operating procedures.

The monitor will discuss the conduct and progress of the study with the investigator and other site staff. The investigator must cooperate with the monitor to ensure that any problems noted in the course of the monitoring are resolved.

9.3 Audit and Inspection of the Study

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

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

10 Ethics

10.1 Regulatory Considerations

The study will be conducted in accordance with the ICH guidelines on GCP, the GCPs applicable to any region where the study is conducted, and the ethical principles set forth in the Declaration of Helsinki. Good clinical practice is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical

studies in a way that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study subjects are protected.

Per GCP, the protocol will be reviewed and approved by the IRB or 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 the subject can withdraw or be withdrawn from the study at any time. Written informed consent will be obtained from each subject prior to the screening procedures to determine if study eligibility criteria are met. A copy of the signed consent form will be given to every subject, and the original will be maintained with the subject's records.

10.2 Institutional Review Board or Independent Ethics Committee

A list of IRB/IEC members or a Statement of GCP Compliance 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(s), 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 investigator of informed consent form changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study; new information that may affect adversely the safety of the subjects or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

10.3 Informed Consent

Freely given informed consent will be obtained and documented for all subjects under this protocol in accordance with the ICH guidelines on GCP, the GCPs applicable to any region where the study is conducted, and the ethical principles set forth in the Declaration of Helsinki.

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

- The study involves research.
- 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.
- 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.
- Who to contact for answers to any questions relating to the research project.
- 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.
- 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.

11 Data Handling and Record Keeping

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a subject's SID or coded number and date of birth. All study records, source medical records, and code sheets or logs linking a subject's name to an SID number will be kept in a secure location. Study records such as CRFs may be maintained electronically and require the same security and confidentiality as paper. Clinical information will not be released without written permission of the subject, except as specified in the informed consent form (eg, necessary for monitoring by regulatory authorities or the sponsor of the clinical study). The investigator must also comply with all applicable privacy regulations (eg, HIPAA 1996, EU Data Protection Directive 95/46/EC).

Study documents (including subject records, copies of data submitted to the sponsor, study notebook, and pharmacy records) must be kept secured. Study documents must not be destroyed without the prior written approval of AstraZeneca.

12 Financing and Insurance

Financing and insurance are addressed in the individual site contracts.

13 Publication Policy

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

14 References

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15 Summary Protocol Amendments and Administrative Changes to the Protocol

Protocol Amendment 1, [redacted]

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

1) Investigator Agreement: removed mention of USA regulations to make the protocol applicable worldwide.

2) General: sections of the protocol were updated to allow subjects to use either fluticasone/salmeterol or budesonide/formoterol and to give budesonide/formoterol dose information.

3) Section 4.2 (Subject Selection): this section was revised to ensure that subjects will be able to provide their own informed consent (ie, without the aid of a legal representative).

4) Section 4.2.1 (Inclusion Criteria): Inclusion Criterion 3 was revised to remove "legal representative".

5) Section 4.2.1 (Inclusion Criteria): Inclusion Criterion 4 was updated to give additional guidance on acceptable methods of birth control.

6) Section 4.2.1 (Inclusion Criteria): Inclusion Criterion 8 (Inclusion Criterion 9 in the original protocol) was updated to remove $FEV_1 \leq 80\%$.

7) Section 4.2.2 (Exclusion Criteria): Exclusion Criterion 11 (Proven H1N1 infection) was removed.

8) Section 4.2.2 (Exclusion Criteria): Exclusion Criterion 26 (Exclusion Criterion 27 in the original protocol) was updated to say "any uncontrolled systemic disease upon physical examination".

9) Section 5.2 (Schedule of Study Procedures), Section 6.1.1 (Adverse Events), Section 10.1 (Regulatory Considerations), Section 10.3 (Informed Consent), Section 11 (Data Handling and Record Keeping): "legal representative" was removed.

10) Section 5.2.2 (Treatment Period): dispensing of fluticasone/salmeterol or budesonide/formoterol was moved from Day 99 to Day 92.

11) Section 5.2.3 (Follow-up Period) and Table 5.2-2 (Schedule of Study Evaluations - Follow-up Period): fluticasone/salmeterol or budesonide/formoterol will be dispensed on Days 204, 232, 260, and 288.

12) Section 5.3.11.12 (Other Disease Evaluations): updated to include guidance on sputum induction, standard collection, and analysis.

13) Section 6.4.1 (Interruption or Permanent Discontinuation of Study Dosing in Individual Subjects): "Proven H1N1 infection during the trial" was removed as this is no longer an exclusion criterion for the study.

14) Section 11 (Data Handling and Record Keeping): updated to reflect AstraZeneca's polices on study document destruction.

Protocol Amendment 2, [redacted]

1) General: various sections of the protocol were updated to properly identify the use of albuterol/salbutamol (instead of albuterol alone) as well as removing IWRS as it is not being used for this study.

2) Section 4.2.1 (Inclusion Criteria): Inclusion Criterion 8 was updated to clarify $FEV_1 \geq 40\%$ must be present at Visit 1 (Day -28) and Visit 3 (Day 1).

3) Section 4.2.1 (Inclusion Criteria): Inclusion Criterion 9 was revised to allow subjects to participate if they have documented history of reversibility or meet the requirements of a methacholine challenge within 36 months before randomization or who partially reversed another opportunity to demonstrate reversibility.

4) Section 4.2.2 (Exclusion Criteria): Exclusion Criterion 7 was updated to clarify a depression score of >15 on the HADS.

5) Section 4.2.2 (Exclusion Criteria): Exclusion Criterion 10 was updated to clarify an active infection is also not allowed during the screening period.

6) Section 4.2.2 (Exclusion Criteria): Exclusion Criterion 25 was updated to clarify a history of tobacco smoking ≥ 10 pack years.

7) Section 4.5.3 (Investigational Product Preparation and administration): updated to reduce the follow-up period after administration of dose from a minimum of 2 hours or until stable to a minimum of 1 hour or until stable after the third dose.

8) Section 5.1 (Efficacy and Clinical Pharmacology Parameters): post-bronchodilator FEV_1 was removed as it is not being performed during the treatment period in the protocol.

9) Section 5.2.1 (Screening): updated to clarify the parameters for when subjects can complete their screening evaluations.

10) Section 5.2.1 (Screening): updated to allow a study window for Visit 2 (Day -14).

11) Section 5.2.2 (Treatment Period): updated to reduce the follow-up period after administration of dose from a minimum of 2 hours or until stable to a minimum of 1 hour or until stable after the third dose.

12) Section 5.2.4 (End of Study Visit): updated to allow a study window for Visit 22 (Day 323)

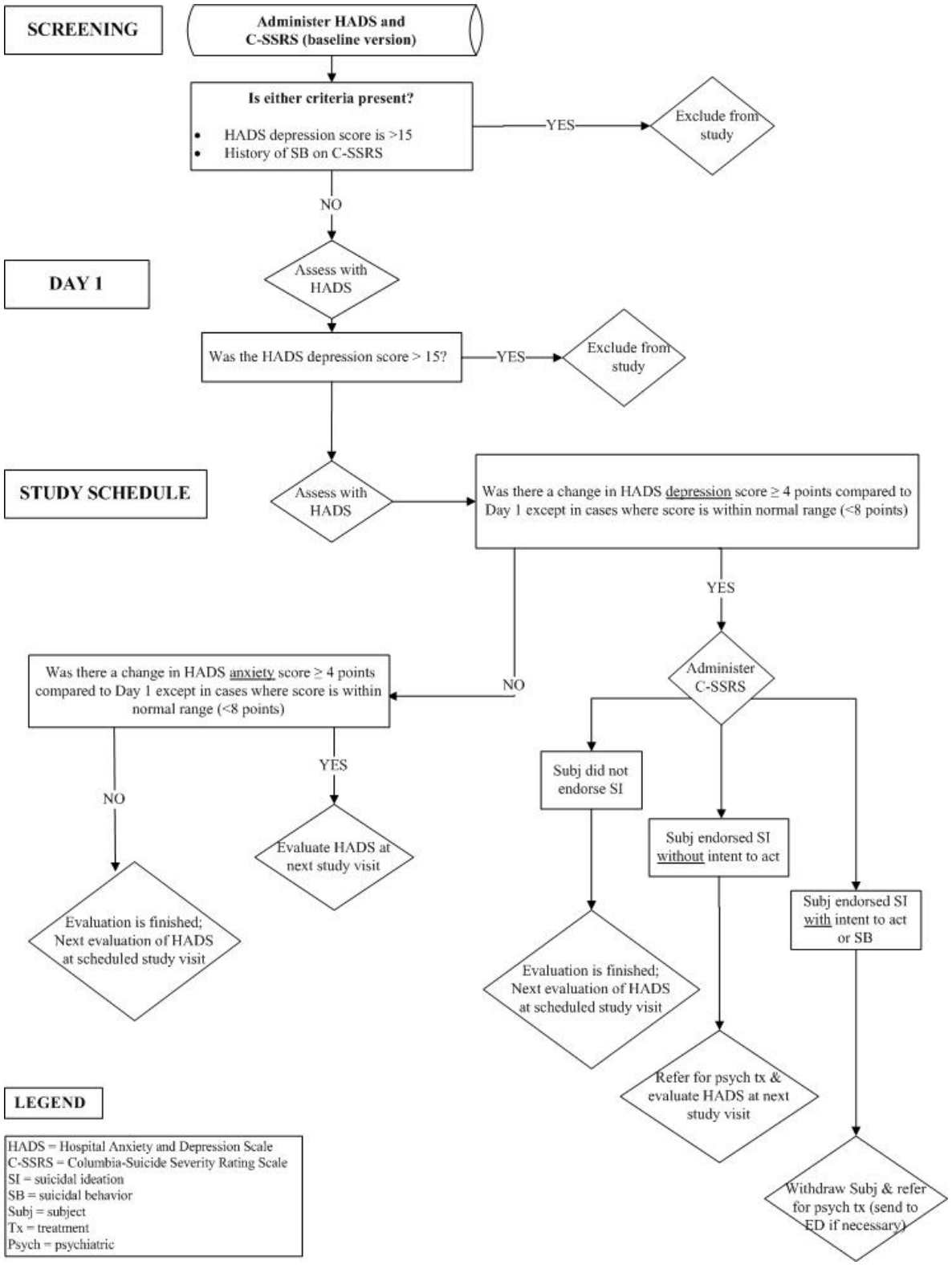
13) Section 5.3.1.2 (The Colombia Suicide Severity Rating Scale) was updated to clarify the C-SSRS must be administered by someone who has received training on the administration of the C-SSRS (eg, investigator or designated site personnel).

14) Section 5.3.3 (Vital Signs): updated to reduce the follow-up period after administration of dose from a minimum of 2 hours or until stable to a minimum of 1 hour or until stable after the third dose.

15) Section 5.3.11.7 (Reversibility of FEV_1): updated to correctly state the number and total dose of albuterol/salbutamol received during the process of determining reversibility.

16) Section 5.3.11.8: (Methacholine Inhalation Challenge Testing): section added to the protocol for subjects who meet all other enrollment criteria except the reversibility criteria. If the subject meets all other eligibility criteria and have a $PC_{20} \leq 8$ mg/mL, then the subject may enter the study.

Appendix 1 Mood and Behavior Assessment Flow Diagram



Appendix 2 Clinical Criteria for Defining Anaphylaxis

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

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

   AND AT LEAST ONE OF THE FOLLOWING

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

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

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

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

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

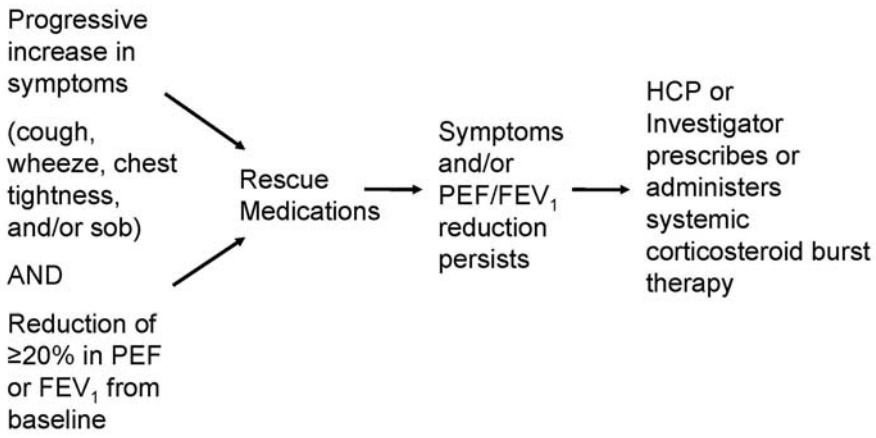
   c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).

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

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

Appendix 3 Proposed Definition for Asthma Exacerbation

MedImmune proposes that an asthma exacerbation, relapse or de novo, be defined as a progressive increase of asthma symptoms (cough, wheeze, chest tightness and/or shortness of breath) AND a reduction of ≥ 20% in PEF or FEV_1 from baseline or best previously measured value prior to the current event that does not resolve after the initiation of rescue medications; and results in a prescription for/or administration of systemic corticosteroid burst therapy by the investigator or health care provider.



An exacerbation event will be considered resolved when the subject's asthma symptoms diminish and PEF or FEV_1 return to > 80% of baseline for ≥ 7 days after completion of systemic corticosteroid burst therapy.

Asthma exacerbation severity will be classified as follows:

- Moderate: Worsening symptoms requiring systemic corticosteroids.
- Severe: Worsening symptoms requiring systemic corticosteroids and hospital admission.

Appendix 4 Asthma Control Questionnaire

Appendix 5 Asthma Quality of Life Questionnaire (Standardized Version)

Appendix 6 Patient Global Impression of Severity

Circle the number that best represents the OVERALL way you have felt about your asthma in the past week:

1 *The best I've ever felt (no problems)*
2 *Pretty good*
3 *Average*
4 *Pretty bad*
5 *The worst I've ever felt*

Appendix 7 The Hospital Anxiety and Depression Scale

Name_____ Date_____

Doctors are aware that emotions play an important role in most illnesses. If your doctor knows about these feelings he will be able to help you more.
This questionnaire is designed to help your doctor to know how you feel. Read each item and place a check in the box that most closely describes how you have been feeling in the past week.
Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

I feel tense or "wound up."
- ❑ Most of the time
- ❑ A lot of the time
- ❑ Time to time, Occasionally
- ❑ Not at all

I still enjoy the things I used to enjoy.
- ❑ Definitely as much
- ❑ Not quite as much
- ❑ Only a little
- ❑ Hardly at all

I get a sort of frightened feeling as if something awful is about to happen.
- ❑ Very definitely and quite badly
- ❑ Yes, but not too badly
- ❑ A little, but it doesn't worry me
- ❑ Not at all

I can laugh and see the funny side of things.
- ❑ As much as I always could
- ❑ Not quite as much now
- ❑ Definitely not so much now
- ❑ Not at all

Worrying thoughts go through my mind.
- ❑ A great deal of the time
- ❑ A lot of the time
- ❑ From time to time but not too often
- ❑ Only occasionally

I feel cheerful.
- ❑ Not at all
- ❑ Not often
- ❑ Sometimes
- ❑ Most of the time

I can sit at ease and feel relaxed.
- ❑ Definitely
- ❑ Usually
- ❑ Not often
- ❑ Not at all

I feel as if I am slowed down.
- ❑ Nearly all the time
- ❑ Very often
- ❑ Sometimes
- ❑ Not at all

I get a sort of frightened feeling, like "butterflies" in the stomach.
- ❑ Not at all
- ❑ Occasionally
- ❑ Quite often
- ❑ Very often

I have lost interest in my appearance.
- ❑ Definitely
- ❑ I don't take as much care as I should
- ❑ I may not take quite as much care
- ❑ I take just as much care as ever

I feel restless if I have to be on the move.
- ❑ Very much indeed
- ❑ Quite a lot
- ❑ Not very much
- ❑ Not at all

I look forward with enjoyment to things.
- ❑ As much as I ever did
- ❑ Rather less than I used to
- ❑ Definitely less than I used to
- ❑ Hardly at all

I get sudden feelings of panic.
- ❑ Very often indeed
- ❑ Quite often
- ❑ Not very often
- ❑ Not at all

I can enjoy a good book or radio or TV program.
- ❑ Often
- ❑ Sometimes
- ❑ Not often
- ❑ Very seldom

Appendix 8 The Columbia Suicide Severity Rating Scale

Appendix 9 Work Productivity and Activity Impairment Questionnaire

Work Productivity and Activity Impairment Questionnaire:
ASTHMA (WPAI:Asthma)

The following questions ask about the effect of your asthma on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your asthma? *Include hours you missed on sick days, times you went in late, left early, etc., because of your asthma. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your asthma affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If asthma affected your work only a little, choose a low number. Choose a high number if asthma affected your work a great deal.

Consider only how much asthma affected productivity while you were working.

Asthma had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Asthma completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your asthma affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If asthma affected your activities only a little, choose a low number. Choose a high number if asthma affected your activities a great deal.

Consider only how much asthma affected your ability to do your regular daily activities, other than work at a job.

Asthma had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Asthma completely prevented me from doing my daily activities

CIRCLE A NUMBER

Appendix 10 Trade Names for Fluticasone/salmeterol and Budesonide/formoterol

Trade Name for Fluticasone/salmeterol	**Country**
Advair®	USA, Canada
Seretide®	EU, Australia, Argentina, Brazil, Colombia, Costa Rica, Panama, Peru, Philippines
Viani®	Germany
ForAir®	India
Trade Name for Budesonide/formoterol	**Country**
Symbicort®	USA, Canada, Argentina, Brazil, Colombia, Costa Rica, Panama, Peru, Philippines

Appendix 11 Classifying Asthma Severity and Initiating Treatment

Components of Severity		Classification of Asthma Severity			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week not daily	Daily	Continuous
	Nighttime Awakenings	≤2x/month	3-4x/month	>1x/week not nightly	Often nightly
Normal FEV_1/FVC **8-19 yr 85%** **20-39 yr 80%** **40-59 yr 75%** **60-80 yr 70%**	SABA use for symptom control	≤2 days/week	>2 days/week not daily	Daily	Several times daily
	Interference with normal activity	none	Minor limitation	Some limitation	Extremely limited
	Lung Function	•Normal FEV_1 between exacerbations • FEV_1 > 80% • FEV_1/FVC normal	• FEV_1 >80% •FEV_1/FVC normal	• FEV_1 >60% but< 80% •FEV_1/FVC reduced 5%	•FEV_1 <60% •FEV_1/FVC reduced> 5%
Risk	Exacerbations (consider frequency and severity)	0-2/year	> 2 /year →		
		Frequency and severity may vary over time for patients in any category			
		Relative annual risk of exacerbations may be related to FEV			
Recommended Step for Initiating Treatment		**Step 1**	**Step 2**	**Step 3**	**Step 4 or 5**
				Consider short course of oral steroids	
		In 2 -6 weeks, evaluate asthma control that is achieved and adjust therapy accordingly			

Appendix 12 Assessing Asthma Control and Adjusting Therapy

Components of Control		Classification of Asthma Control		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
IMPAIRMENT	Symptoms	≤ 2 days/week	> 2 days/week	Throughout the day
	Nighttime awakenings	≤ 2/month	1-3/week	≥ 4/week
	Interference with normal activity	none	Some limitation	Extremely limited
	SABA use	≤ 2 days/week	> 2 days/week	Several times/day
	FEV_1 or peak flow	> 80% predicted/ personal best	60-80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires ATAQ/ACT	0/≥ 20	1-2/16-19	3-4/≤ 15
RISK	Exacerbations	0- 1 per year	2 - 3 per year	> 3 per year
	Progressive loss of lung function	Evaluation requires long-term follow up care		
	Rx-related adverse effects	Consider in overall assessment of risk		
Recommended Action For Treatment		•Maintain current step •Consider step down if well controlled at least 3 months	•Step up 1 step •Reevaluate in 2 - 6 weeks	•Consider oral steroids •Step up 1-2 weeks and reevaluate in 2 weeks

Appendix 13 Estimated Comparative Daily Dosages for Inhaled Corticosteroids

Drug	Low Daily Dose Adult	Medium Daily Dose Adult	High Daily Dose Adult
Beclamethazone HFA 40 or 80 mcg/puff	80-240 mcg	>240-480 mcg	>480 mcg
Budesonide DPI 90, 180, or 200 mcg/inhalation	180-600 mcg	>600-1,200 mcg	>1,200 mcg
Flunisolide 250 mcg/puff	500-1,000 mcg	>1,000-2,000 mcg	>2,000 mcg
Flunisolide HFA 80 mcg/puff	320 mcg	>320-640 mcg	>640 mcg
Fluticasone **HFA/MDI:** 44, 110, or 220 mcg/puff **DPI:** 50, 100, or 250 mcg/puff	88-264 mcg 100-300 mcg	>264-440 mcg >300-500 mcg	>440 mcg >500 mcg
Mometasone DPI 200 mcg/inhalation	200 mcg	400 mcg	>400 mcg
Triamcinolone acetonide 75 mcg/puff	300-750 mcg	>750-1,500 mcg	>1,500 mcg