A Phase 2 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI9929 in Adult Subjects with Inadequately Controlled, Severe Asthma

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Protocol Synopsis

TITLE

A Phase 2 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI9929 in Adult Subjects with Inadequately Controlled, Severe Asthma

HYPOTHESES

The primary hypothesis is that inhibition of thymic stromal lymphopoietin (TSLP) by MEDI9929, when given SC at doses of 280 mg every 2 weeks (Q2W), 210 mg every 4 weeks (Q4W), or 70 mg Q4W when compared to placebo over a 52-week treatment period, improves asthma control by reducing asthma exacerbations in adult subjects with inadequately controlled, severe asthma (Global Initiative for Asthma [GINA] Step 4 or 5).

The secondary hypotheses are:

- Inhibition of TSLP by MEDI9929 improves efficacy in at least one of the following subpopulations of asthma:
  - Eosinophilic asthma: defined for this study as a screening blood eosinophil count of ≥ 250 cells/μL from the site's local laboratory.
  - T helper cell (Th)2 inflammation: defined for this study as a screening blood eosinophil count ≥ 140 cells/μL from the site's local laboratory and a screening total serum immunoglobulin E (IgE) level of > 100 IU/mL (Corren et al, 2011).
  - Elevated fraction of exhaled nitric oxide (FE_{NO}): defined for this study as a baseline FE_{NO} measurement ≥ to the median from all randomized subjects in the study.
  - Elevated serum periostin level: defined for this study as a baseline serum periostin level ≥ to the median from all randomized subjects in the study.
  - Current post-bronchodilator (BD) forced expiratory volume in 1 second (FEV_1) reversibility: defined as a post-BD change in FEV_1 of ≥ 12% and ≥ 200 mL demonstrated at one of the screening visits (Visit 1 [Week -5], Visit 2 [Week -4], or Visit 3 [Week -1]).
  - Allergic asthma: defined for this study as a baseline positive IgE fluorescence enzyme immunoassay level to one or more region-specific allergens.
- That inhibition of TSLP by MEDI9929 improves lung function, asthma symptoms, and quality of life in adult subjects with inadequately controlled, severe asthma.
- MEDI9929 is well tolerated when given SC at doses of 280 mg Q2W, 210 mg Q4W, or 70 mg Q4W as compared to placebo over a 52-week treatment period.

OBJECTIVES

Primary:

To evaluate the effect of 3 dose levels of MEDI9929 on asthma exacerbations in adult subjects with inadequately controlled, severe asthma

Secondary:

1) To evaluate the effect of MEDI9929 on asthma exacerbations, lung function, and asthma symptoms in the pre-specified subpopulations of asthma.
2) To evaluate the effect of MEDI9929 on lung function.
3) To assess the effect of MEDI9929 on asthma symptoms and other metrics related to asthma control.
4) To assess the effect of MEDI9929 on other parameters of asthma exacerbations.
5) To determine the optimal dose and regimen of MEDI9929 to be used in later studies.
6) To assess the effect on MEDI9929 on health-related quality of life (HRQoL).
7) To evaluate the safety and tolerability of MEDI9929.
8) To describe the pharmacokinetics (PK) and immunogenicity (IM) of MEDI9929.

STUDY ENDPOINTS

Primary:

The primary endpoint for this study is the annualized asthma exacerbation rate (AER) measured at Week 52

Secondary:

1. Reduction in AER, change from baseline in FEV_1, and change from baseline in overall symptom score will be evaluated at Week 52 in the following pre-specified subpopulations of asthma: 1) eosinophilic and non-eosinophilic; 2) Th2 high/low 3) FE_{NO} high/low; 4) periostin high/low; 5) current post-BD FEV_1 reversibility; and 6) allergic and non-allergic.
2. Change from baseline in lung function as measured by pre-BD and post-BD FEV_1 and forced vital capacity (FVC) at Week 52 in the overall population.
3. Change from baseline in asthma symptoms (daytime and nighttime symptom frequency and severity, activity avoidance and limitation, asthma-related stress and fatigue as well as rescue asthma medication use) as measured by the Asthma Daily Diary, and other measures of asthma control as measured by the Asthma Control Questionnaire omitting FEV_1 (ACQ-6) at Week 52 in the overall population.
4. Annualized rate of hospitalizations due to asthma (ie, severe asthma exacerbations), time to first asthma exacerbation/severe asthma exacerbation, and proportion of subjects with one or more asthma exacerbations/severe asthma exacerbations at Week 52.
5. A dose- and exposure-response analysis will be done at Week 52 on reduction in AER, change from baseline in FEV_1, and change from baseline in overall symptom score to determine the optimal dose and regimen of MEDI9929.
6. Change from baseline in Asthma Quality of Life Questionnaire (Standardised; AQLQ[S])+12 and European Quality of Life - 5 Dimensions 5 Level Version (EQ-5D-5L) at Week 52.
7. Treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), vital signs, laboratory assessments, and electrocardiogram (ECG) during the study (Week 0 [Day 1] to Week 64).
8. MEDI9929 PK and anti-drug antibodies (ADA) during the study (Week 0 [Day 1] to Week 64).

STUDY DESIGN

This is a Phase 2, multicenter, multinational, dose-ranging, double-blind, randomized, parallel-arm, placebo-controlled study to evaluate the effect of 3 dose levels of MEDI9929 on the AER in adult subjects with inadequately controlled, severe asthma. Approximately 110 study centers will participate in the study. Subjects will have a history of at least 2 exacerbations or at least 1 severe asthma exacerbation resulting in hospitalization (admission to the hospital for at least 24 hours) in the past year on background asthma therapy of medium- or high-dose inhaled corticosteroids (ICS) and long-acting β2 agonist (LABA), with or without additional asthma controller medications (leukotriene receptor antagonists [LTRA], long-acting anti-muscarinics [LAMA], cromones, and theophylline and/or maintenance oral corticosteroids [OCS]) from screening through the safety follow-up period at Week 64. The cost of the ICS and LABA treatment will be reimbursed to the sites by the sponsor for the duration of study participation, where applicable.

Approximately 552 subjects will be randomized in the study, with approximately 85% of the total number of subjects designated as non-Japanese subjects (ie, subjects enrolled at sites outside of Japan) and approximately 15% of the total number of subjects designated as Japanese subjects (ie, subjects enrolled at sites in Japan).

Additionally, at least 50% of the subjects in the study will be currently reversible, ie post-BD change in FEV_1 of $\geq$ 12% and $\geq$ 200 mL demonstrated at one of the screening visits (Visit 1 [Week -5], Visit 2 [Week -4], OR Visit 3 [Week -1]).

Total enrollment in the study may exceed 552 subjects depending on whether additional non-Japanese subjects are enrolled to mitigate for slow enrollment in Japan, and to accommodate subjects in screening/run-in when the different strata are closed to enrollment.

Prior to randomization, subjects will be stratified by study site (non-Japanese and Japanese), and then blood eosinophil count ($\geq$ or < 250 cells/μL) and by ICS dose level (medium or high). Subjects taking maintenance OCS will be automatically assigned to the high-dose ICS strata. There will be a total of 8 strata; 4 strata for non-Japanese subjects and 4 identical strata for Japanese subjects. Subjects will be stratified as follows:

- High blood eosinophil count (≥ 250 cells/μL) and medium ICS dose level
- High blood eosinophil count (≥ 250 cells/μL) and high ICS dose level
- Low blood eosinophil count (< 250 cells/μL) and medium ICS dose level
- Low blood eosinophil count (< 250 cells/μL) and high ICS dose level

At least 50% of the total subjects will be enrolled in the high blood eosinophil stratum (≥ 250 cells/μL), and at least 40% of the subjects in each blood eosinophil stratum will be enrolled in high-dose ICS stratum. Because of the complexity of having 3 strata in the interactive voice/web response system (IXRS), this protocol will not stratify by current post-BD FEV_1 reversibility, but will require that at least 50% of the study population demonstrate current post-BD FEV_1 reversibility.

After stratification, subjects will be randomized in a 1:1:1:1 ratio to receive one of 3 dose levels of SC MEDI9929 (280 mg Q2W, 210 mg Q4W, or 70 mg Q4W) or placebo Q2W for 52 weeks. In the event that enrollment of the Japanese subjects is delayed, non-Japanese sites may be permitted to continue to enroll subjects to reach the required sample size for the Stage I analysis. In this event, the overall number of subjects in the study will increase in order for sites in Japan to meet the enrollment goal. After the required number of subjects have been enrolled for the Stage I analysis, the requirement for stratification by medium- or high-dose ICS will be removed in order to facilitate enrollment of the remainder of the Japanese subjects into the study.

An ECG sub-study will be done in subgroup of subjects to confirm that MEDI9929 does not affect cardiac electrophysiological intervals. Additionally, flow cytometry will be performed at selected sites to evaluate intracellular cytokines in T cells by flow cytometry following ex vivo stimulation by phorbol myristate acetate.

An independent Data and Safety Monitoring Board (DSMB) will perform evaluations of safety data at specified regular intervals throughout the study and make recommendations to the sponsor regarding further conduct of the study. After reviewing the data by treatment group, the DSMB may request that a treatment group be unblinded for additional review.

Subjects will be in this study for approximately 1.3 years (69 weeks), which includes a screening/run-in period of up to approximately 5 weeks, a 52-week treatment period, and a 12-week post-treatment follow-up period. The last dose of investigational product will be administered at Week 50.

TARGET SUBJECT POPULATION

Subjects will have a history of at least 2 exacerbations or at least 1 severe asthma exacerbation resulting in hospitalization (admission to the hospital for at least 24 hours) in the past year on background asthma therapy of medium- or high-dose ICS and LABA, with or without additional asthma controller medications (LTRA, LAMA, cromones, and theophylline and/or maintenance OCS) from screening through the safety follow-up period at Week 64. The cost of the ICS and LABA treatment will be reimbursed to the sites by the sponsor for the duration of study participation, where applicable.

INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

Subjects will receive one of 3 SC dose levels of MEDI9929 (280 mg Q2W, 210 mg Q4W, or 70 mg Q4W) or SC placebo for 52 weeks. All subjects will receive 3 injections (2 × 1.5 mL and 1 × 1.0 mL) Q2W in order to maintain the blinding of the different doses.

STATISTICAL ANALYSIS PLAN

The primary endpoint will be tested using a stepdown method for 3 hypotheses (from the high dose [280 mg Q2W] to the medium dose [210 mg Q4W] to the low dose [70 mg Q4W] when compared with placebo) to maintain the overall type-1 error rate at 0.1 (two sided), and will be analyzed using a negative binomial regression model with treatment group, baseline blood eosinophil count (≥ or < 250 cells/μL), and baseline ICS dose level (medium or high) as covariates. Nominal p-values will be provided for the selected secondary efficacy endpoints (pulmonary function, ACQ-6, AQLQ(S)+12, and Asthma Daily Diary) without multiplicity adjustment. For selected secondary efficacy endpoints that are continuous variables, a generalized linear mixed model using a linear contrast test including treatment group, visit, treatment-by-visit interaction, baseline blood eosinophil count (≥ or < 250 cells/μL), baseline ICS dose level (medium or high), and the respective baseline measure for the given endpoint as fixed effects may be used to compare the change from baseline at Week 52 for each efficacy endpoint between the individual MEDI9929 dose groups and the placebo group, respectively.

Two formal analyses (Stage I analysis and Stage II analysis) and an interim analysis are planned for the study. The Stage I analysis will be conducted after approximately 552 subjects have completed the Week 52 visit. The

primary analysis for which the study is powered will be completed in the Stage I analysis, and long-term safety will be assessed in the Stage II analysis. An interim analysis will be conducted after approximately 552 subjects have completed the Week 28 visit. The objective of this interim analysis is to accelerate decisions on future development options for MEDI9929.

Sample size calculations have been performed for the primary endpoint of annualized AER, based on the negative binomial distribution (Keene et al, 2007). Approximately 552 subjects will be randomized in the study, with approximately 85% of the total number of subjects designated as non-Japanese subjects (ie, subjects enrolled at sites outside of Japan) and approximately 15% of the total number of subjects designated as Japanese subjects (ie, subjects enrolled at sites in Japan). A total of 124 subjects per treatment group would be required to detect a 40% reduction in the annual AER for each MEDI9929 dose group compared to placebo group, assuming an AER of 0.7 in the placebo group, a two sided significance level of 0.1, 80% power, and a dispersion parameter of 0.7 based on the negative binomial distribution. The AER of 0.7 in the placebo group was estimated based on internal and external studies with a similar subject population (before considering dropouts). The dispersion parameter of 0.7 was selected from the mepolizumab study in subjects with severe, eosinophilic asthma (Pavord et al, 2012). Sample size was increased to 138 per treatment group to accommodate a 10% loss of information due to dropouts. The minimal detectable difference is approximately 28% reduction in annual AER.

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibodies
ACQ-6	Asthma Control Questionnaire, omitting forced expiratory volume in one second (FEV_1)
AE	adverse event
AER	asthma exacerbation rate
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AQLQ(S)+12	Asthma Quality of Life Questionnaire (Standardised)
ATS	American Thoracic Society
BALF	bronchoalveolar lavage fluid
BCG	Bacillus Calmette Guérin
BD	bronchodilator
BP	blood pressure
CI	confidence interval
CRO	contract research organization
CTCAE v4.03	Common Terminology Criteria for Adverse Events, version 4.03
CXR	chest x-ray
DSMB	Data and Safety Monitoring Board
DNA	deoxyribonucleic acid
DPI	dry powder inhaler
eCRF	electronic case report form
EAR	early asthmatic response
ECG	electrocardiogram
ED	emergency department
EDV	early discontinuation visit
ePRO	electronic patient-reported outcome
EQ-5D-5L	European Quality of Life - 5 Dimensions 5 Level Version
ERS	European Respiratory Society
EU	European Union
EXACA	exacerbation eCRF
FEIA	fluorescence enzyme immunoassay
FE_{NO}	fraction of exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice

Abbreviation or Specialized Term	Definition
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRU	healthcare resource utilization
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	inhaled corticosteroid(s)
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
IM	immunogenicity
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IXRS	interactive voice/web response system
LABA	long-acting β2 agonist
LAMA	long-acting anti-muscarinics
LAR	late asthmatic response
LTRA	leukotriene receptor antagonist
mAb	monoclonal antibody
MDI	metered dose inhaler
NOAEL	no-observed-adverse-effect-level
OCS	oral corticosteroids
PD	pharmacodynamic
PEFR	peak expiratory flow rate
PK	pharmacokinetic(s)
post-BD	post-bronchodilator
PP	per protocol
PPD	purified protein derivative
pre-BD	pre-bronchodilator
PRO	patient reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks
Q7D	every 7 days
Q14D	every 14 days
Q28D	every 28 days
QFT-G	QuantiFERON® -tuberculosis Gold

Abbreviation or Specialized Term	Definition
SABA	short-acting β2 agonist
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SFV	safety follow-up visit
SID	subject identification
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
Th	T helper cell
TSLP	thymic stromal lymphopoietin
TSLPR	thymic stromal lymphopoietin receptor
ULN	upper limit of normal
USA	United States of America
WPAI+CIQ	Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions

1 INTRODUCTION

1.1 Disease Background

Asthma is a chronic inflammatory disease in the airways characterized by bronchial hyperreactivity and reversible airflow limitation that causes wheezing, shortness of breath, cough, and chest tightness. International treatment guidelines such as Global Initiative for Asthma (GINA; GINA, 2012) recommend inhaled corticosteroids (ICS) as first-line therapy for persistent asthma. For those patients who are symptomatic and on ICS alone, the addition of a long-acting β2 agonist (LABA) is the current treatment of choice. However, there are a number of asthmatic patients who are still symptomatic despite treatment with ICS and LABA combinations (Rabe et al, 2004). Treatment options then include the addition of other controller therapies including leukotriene antagonists, theophylline, and oral corticosteroids (OCS). Xolair® (omalizumab) may be suitable for a subgroup of patients with proven reactivity to an aeroallergen and elevated serum immunoglobulin E (IgE) levels.

Approximately 5% to 10% of asthma patients have severe asthma, which may be inadequately controlled by ICS and LABA combinations together with additional controller therapies (Brightling et al, 2008). These patients are at increased risk of asthma exacerbations (Tough et al, 1998; Turner et al, 1998) and have the greatest medical need among the asthmatic population today and represent the greatest economic cost (> 50% of total asthma-related health care costs; Antonicelli et al, 2004; Serra-Batlles et al, 1998; Barnes and Kuitert, 1996).

Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine that is produced in response to proinflammatory stimuli (eg, infectious and environmental stimuli) and drives allergic inflammatory responses, primarily through its activity on dendritic and mast cells (Gilliet et al, 2003; Soumelis et al, 2002; Reche et al, 2001; Allakhverdi et al, 2007). Human TSLP expression is reported to be increased in asthmatic airways correlating with disease severity (Ying et al, 2005). The TSLP protein levels are detectable in the concentrated bronchoalveolar lavage fluid (BALF) of patients with asthma. There are also emerging data that TSLP mediates non-allergic (non-T helper cell [Th]2) inflammation (Tanaka et al, 2009; Ziegler et al, 2013). Additionally, preclinical data support the role of TSLP in asthma. These data suggest that targeting TSLP may serve to suppress multiple biological pathways involved in asthma, including but not limited to those involving interleukin (IL)-4 and IL-13. Targeting TSLP may result in improved asthma control in patients with severe asthma.

1.2 MEDI9929 Background

MEDI9929 (formerly AMG 157) is briefly described below. Refer to the current Investigator's Brochure for details.

MEDI9929 is a human immunoglobulin G (IgG) 2λ monoclonal antibody (mAb) directed against TSLP, expressed in the Chinese hamster ovary cell CS-9 cell line. The molecule is a heterotetramer consisting of 2 heavy chains of the IgG2 subclass and 2 light chains of the lambda subclass, which are covalently linked through disulfide bonds. MEDI9929 binds human TSLP and prevents its interaction with thymic stromal lymphopoietin receptor (TSLPR). MEDI9929 is able to bind both human and cynomolgus monkey TSLP with high affinity (equilibrium dissociation constant = 15.8 and 32.2 pM, respectively). Since TSLP is involved in the pathogenesis of asthma, inhibition of this cytokine may provide benefit to patients with asthma.

1.3 Summary of Nonclinical Experience

MEDI9929 binds to human and cynomolgus monkey TSLP with picomolar affinity, and neutralized human and cynomolgus monkey TSLP with subnanomolar potency. MEDI9929 did not cross react with mouse, rat, or rabbit TSLP and therefore a surrogate antibody (anti-mouse TSLP mAb [M702]) was utilized to demonstrate in vivo efficacy and to identify biomarkers in preclinical models of inflammation in the lung and skin. Effects of MEDI9929 on cardiovascular, respiratory, and neurobehavioral endpoints were evaluated in telemetered cynomolgus monkeys. MEDI9929 administered as a single intravenous (IV) dose of 300 mg/kg was well tolerated. There were no treatment-related effects on cardiovascular function, respiratory rate, neurological behavior, and body temperature.

MEDI9929 was evaluated in repeated-dose studies in cynomolgus monkeys at doses up to 300 mg/kg administered subcutaneously (SC) every 7 days (Q7D) for 1, 3, and 6 months; at up to 300 mg/kg IV Q7D for 1 month; and at 50 mg/kg IV Q7D for 6 months. The no-observed-adverse-effect-level (NOAEL) was the highest dose tested for each route of administration in each study. In the maternal, embryo-fetal, and neonatal toxicity study, pregnant female cynomolgus monkeys were dosed Q7D at 50 or 300 mg/kg IV from early gestation through delivery. There were no adverse effects of MEDI9929 on maternal health, pregnancy outcome, embryo-fetal development, or neonatal development up to 6.5 months of age.

1.4 Summary of Clinical Experience

MEDI9929 has been evaluated in 2 completed Phase 1 clinical studies conducted in the United States of America (USA; Studies 20070620 and 20080390), and one completed Phase 1 clinical study conducted in Canada (Study 20101183).

Study 20070620 was a first-time-in-human, randomized, double-blind, placebo-controlled, ascending single-dose study for MEDI9929 (2.1, 7, 21, 70, 210, or 420 mg SC, or 210 or 700 mg IV) in healthy subjects and subjects with moderate to severe atopic dermatitis. Study 20080390 was a randomized, multiple-dose, double-blind, placebo-controlled, sequential dose-escalation study for MEDI9929 (35, 105, or 210 mg SC once every 28 days [Q28D] for a total of 3 doses, 210 mg SC once every 14 days [Q14D] for a total of 6 doses, 210 mg SC Q7D for a total of 12 doses, or 700 mg IV Q28D for a total of 3 doses) administered to healthy subjects. Safety results demonstrated an acceptable safety profile in healthy subjects and subjects with atopic dermatitis. No subjects who received MEDI9929 were positive for anti-drug antibodies (ADA) to MEDI9929.

Study 20101183 was a randomized, double-blind, placebo-controlled, parallel-design, multiple-dose study to evaluate the late asthmatic response (LAR) after an inhaled allergen challenge in 31 adult subjects with mild atopic asthma who received up to 3 IV infusions of 700 mg MEDI9929 or placebo on days 1, 29, and 57. Safety data indicated that a total of 15 out of 16 subjects (93.8%) in the MEDI9929 group and 12 out of 15 subjects (80.0%) in the placebo group experienced a treatment-emergent adverse event (TEAE). No deaths or treatment-emergent serious adverse events (TESAEs) were reported. One subject in the MEDI9929 group withdrew from investigational product due to a TEAE of worsening asthma; the event was considered by the investigator to be unrelated to investigational product. Efficacy results from this study demonstrated that MEDI9929 significantly inhibited the LAR after inhaled allergen challenge. In addition, there were decreases in the early asthmatic response (EAR), in fraction of exhaled nitric oxide (FE_{NO}), in blood and sputum eosinophils, and in the Th2/ Th1 balance based upon a new exploratory biomarker assay.

1.5 Rationale for Conducting the Study

Efficacy results from the inhaled allergen challenge clinical study (Study 20101183) suggest that MEDI9929 is pharmacologically active in subjects with asthma. Since there is a medical need for new therapies to reduce the number and severity of asthma exacerbations and to improve asthma control in patients with severe asthma who are unable to gain complete asthma control using currently available therapies (eg, ICS and LABA combinations together with additional controller therapies), a Phase 2 clinical study is being conducted to evaluate

the efficacy of 3 dose levels of MEDI9929 in this target population. The information gained from this study will have significant value in determining whether MEDI9929 has the potential to be developed as therapy for these patients. Results from this study will also form the basis for decisions for design for future studies.

Clinical and nonclinical experience with MEDI9929 demonstrates no safety or tolerability concerns to date. Potential risks based on the mechanism of action of MEDI9929 include immune complex disease, serious infections, and hypersensitivity and allergic reactions. Risk minimization strategies associated with MEDI9929 have been identified and are described in the current Investigator's Brochure and are included in the protocol. Additional risks associated with the conduct of the study (eg, collection of blood for safety, pharmacokinetics (PK), and pharmacodynamic (PD) assessments and spirometry testing) do not have a significant impact on the study. Given that appropriate measures have been instituted in this study to protect subjects from the possible risks, the results of the inhaled allergen challenge clinical study, and the unmet medical need for the target population, the current risk-benefit profile appears favorable and justifies the administration of MEDI9929 in this study.

1.6 Research Hypotheses

1.6.1 Primary Hypothesis

The primary hypothesis is that inhibition of TSLP by MEDI9929, when given SC at doses of 280 mg every 2 weeks (Q2W), 210 mg every 4 weeks (Q4W), or 70 mg Q4W when compared to placebo over a 52-week treatment period, improves asthma control by reducing asthma exacerbations in adult subjects with inadequately controlled, severe asthma (GINA Step 4 or 5; GINA, 2012).

1.6.2 Secondary Hypotheses

The secondary hypotheses are:

- Inhibition of TSLP by MEDI9929 improves efficacy in at least one of the following subpopulations of asthma:
  - Eosinophilic asthma: defined for this study as a screening blood eosinophil count of ≥ 250 cells/µL from the site's local laboratory.
  - Th2-type inflammation: defined for this study as a screening blood eosinophil count ≥ 140 cells/µL from the site's local laboratory and a screening total serum IgE level of > 100 IU/mL (Corren et al, 2011).
  - Elevated FE_{NO}: defined for this study as a baseline FE_{NO} measurement ≥ to the median from all randomized subjects in the study.

- Elevated serum periostin level: defined for this study as a baseline serum periostin level ≥ to the median from all randomized subjects in the study.
- Current post-bronchodilator (BD) forced expiratory volume in 1 second (FEV_1) reversibility: defined as a post-BD change in FEV_1 of ≥ 12% and ≥ 200 mL demonstrated at one of the screening visits (Visit 1 [Week -5], Visit 2 [Week -4], or Visit 3 [Week -1]).
- Allergic asthma: defined for this study as a baseline positive IgE fluorescence enzyme immunoassay (FEIA) level to one or more region-specific allergens.

- That inhibition of TSLP by MEDI9929 improves lung function, asthma symptoms, and quality of life in adult subjects with inadequately controlled, severe asthma.
- MEDI9929 is well tolerated when given SC at doses of 280 mg Q2W, 210 mg Q4W, or 70 mg Q4W as compared to placebo over a 52-week treatment period.

2 OBJECTIVES

2.1.1 Primary Objective

To evaluate the effect of 3 dose levels of MEDI9929 on asthma exacerbations in adult subjects with inadequately controlled, severe asthma

2.1.2 Secondary Objectives

1. To evaluate the effect of MEDI9929 on asthma exacerbations, lung function, and asthma symptoms in the pre-specified subpopulations of asthma.
2. To evaluate the effect of MEDI9929 on lung function.
3. To assess the effect of MEDI9929 on asthma symptoms and other metrics related to asthma control.
4. To assess the effect of MEDI9929 on other parameters of asthma exacerbations.
5. To determine the optimal dose and regimen of MEDI9929 to be used in later studies.
6. To assess the effect on MEDI9929 on health-related quality of life (HRQoL).
7. To evaluate the safety and tolerability of MEDI9929.
8. To describe the PK and immunogenicity (IM) of MEDI9929.

2.1.3 Exploratory Objectives

1. To evaluate the effect of MEDI9929 on other efficacy outcomes in the pre-specified subpopulations of asthma.
2. To evaluate the effect of MEDI9929 on healthcare resource utilization (HRU), work productivity, and health status.
3. To assess the relationship of baseline biomarkers to MEDI9929 response (efficacy outcomes) and to assess the effect of MEDI9929 on biomarkers.

4. To collect and evaluate deoxyribonucleic acid (DNA) for research into genes/genetic variation that may influence clinical response to MEDI9929.

2.2 Study Endpoints

2.2.1 Primary Endpoint

The primary endpoint for this study is the annualized asthma exacerbation rate (AER) measured at Week 52 (see Section 4.3.1.1 for asthma exacerbation definition).

2.2.2 Secondary Endpoints

1. Reduction in AER, change from baseline in FEV_1, and change from baseline in overall symptom score will be evaluated at Week 52 in the following pre-specified subpopulations of asthma: 1) eosinophilic and non-eosinophilic; 2) Th2 high/low 3) FE_{NO} high/low; 4) periostin high/low; 5) current post-BD FEV_1 reversibility; and 6) allergic and non-allergic.
2. Change from baseline in lung function as measured by pre-BD and post-BD FEV_1 and forced vital capacity (FVC) at Week 52 in the overall population.
3. Change from baseline in asthma symptoms (daytime and nighttime symptom frequency and severity, activity avoidance and limitation, asthma-related stress and fatigue as well as rescue asthma medication use) as measured by the Asthma Daily Diary, and other measures of asthma control as measured by the Asthma Control Questionnaire omitting FEV_1 (ACQ-6) at Week 52 in the overall population.
4. Annualized rate of hospitalizations due to asthma (ie, severe asthma exacerbations), time to first asthma exacerbation/severe asthma exacerbation, and proportion of subjects with one or more asthma exacerbations/severe asthma exacerbations at Week 52.
5. A dose- and exposure-response analysis will be done at Week 52 on reduction in AER, change from baseline in FEV_1, and change from baseline in overall symptom score to determine the optimal dose and regimen of MEDI9929.
6. Change from baseline in Asthma Quality of Life Questionnaire (Standardised; AQLQ[S])+12 and European Quality of Life - 5 Dimensions 5 Level Version (EQ-5D-5L) at Week 52.
7. TEAEs, TESAEs, vital signs, laboratory assessments, and electrocardiogram (ECG) during the study (Week 0 [Day 1] to Week 64).
8. MEDI9929 PK and ADA during the study (Week 0 [Day 1] to Week 64).

2.2.3 Exploratory Endpoints

1. Other efficacy outcomes, including change from baseline in ACQ-6, AQLQ(S)+12, and total rescue medication use, will be evaluated at Week 52 in the following subpopulations of asthma: 1) eosinophilic and non-eosinophilic; 2) Th2 high/low (Corren et al, 2011); 3) FE_{NO} high/low; 4) periostin high/low; 5) current post-BD FEV_1 reversibility; and 6) allergic and non-allergic.

2. Reduction in AER and change from baseline in lung function, asthma symptoms, asthma control, and HRQoL will be evaluated to Week 64.
3. HRU as assessed by the investigator or designee; work productivity as measured by Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ) during the study (Week 0 [Day 1] to Week 64).
4. Biomarkers related to asthma or the TSLP pathway, including blood biomarkers, intracellular cytokines in *ex vivo* activated blood T cells evaluated by flow cytometry, and FE_{NO}. The association between these baseline biomarkers and response (efficacy outcomes) will be explored.
5. Analysis of DNA samples for gene polymorphisms that may affect clinical response to MEDI9929 and also estimate the prevalence of these polymorphisms.

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This is a Phase 2, multicenter, multinational, dose-ranging, double-blind, randomized, parallel-arm, placebo-controlled study to evaluate the effect of 3 dose levels of MEDI9929 on the AER in adult subjects with inadequately controlled, severe asthma. Approximately 110 study centers will participate in the study. Subjects will have a history of at least 2 exacerbations or at least 1 severe asthma exacerbation resulting in hospitalization (admission to the hospital for at least 24 hours) in the past year on background asthma therapy of medium- or high-dose ICS and LABA, with or without additional asthma controller medications (leukotriene receptor antagonists [LTRA], long-acting anti-muscarinics [LAMA], cromones, and theophylline and/or maintenance OCS) from screening through the safety follow-up period at Week 64. The cost of the ICS and LABA treatment will be reimbursed to the sites by the sponsor for the duration of study participation, where applicable.

Approximately 552 subjects will be randomized in the study, with approximately 85% of the total number of subjects designated as non-Japanese subjects (ie, subjects enrolled at sites outside of Japan) and approximately 15% of the total number of subjects designated as Japanese subjects (ie, subjects enrolled at sites in Japan). Additionally, at least 50% of the subjects in the study will be currently reversible; ie post-BD change in FEV_1 of $\geq$ 12% and $\geq$ 200 mL demonstrated at one of the screening visits (Visit 1 [Week -5], Visit 2 [Week -4], OR Visit 3 [Week -1]).

Total enrollment in the study may exceed 552 subjects depending on whether additional non-Japanese subjects are enrolled to mitigate for slow enrollment in Japan, and to accommodate subjects in screening/run-in when the different strata are closed to enrollment.

Prior to randomization, subjects will be stratified by study site (non-Japanese and Japanese), and then blood eosinophil count (≥ or < 250 cells/μL) and by ICS dose level (medium or high). Subjects taking maintenance OCS will be automatically assigned to the high-dose ICS strata. There will be a total of 8 strata; 4 strata for non-Japanese subjects and 4 identical strata for Japanese subjects. Subjects will be stratified as follows:

- High blood eosinophil count (≥ 250 cells/μL) and medium ICS dose level
- High blood eosinophil count (≥ 250 cells/μL) and high ICS dose level
- Low blood eosinophil count (< 250 cells/μL) and medium ICS dose level
- Low blood eosinophil count (< 250 cells/μL) and high ICS dose level

At least 50% of the total subjects will be enrolled in the high blood eosinophil stratum (≥ 250 cells/μL), and at least 40% of the subjects in each blood eosinophil stratum will be receiving high-dose ICS. Once the required number of subjects has been enrolled into a stratum, any subjects already in screening/run-in may be enrolled into that stratum if eligible. The stratum will then be closed, and no further subjects will be enrolled into it.

After stratification, subjects will be randomized in a 1:1:1:1 ratio to receive one of 3 dose levels of SC MEDI9929 (280 mg Q2W, 210 mg Q4W, or 70 mg Q4W) or placebo Q2W for 52 weeks (Figure 3.1.1-1). In the event that enrollment of the Japanese subjects is delayed, non-Japanese sites may be permitted to continue to enroll subjects to reach the required sample size for the Stage I analysis (see Section 4.8.7). In this event, the overall number of subjects in the study will increase in order for sites in Japan to meet the 15% Japanese enrollment goal. After the required number of subjects have been enrolled for the Stage I analysis, the requirement for stratification by medium- or high-dose ICS will be removed in order to facilitate enrollment of the remainder of the Japanese subjects into the study.

There will be an interim analysis after approximately 552 subjects have completed the Week 28 visit. The objective of this interim analysis is to accelerate decisions on future development options for MEDI9929. No futility analysis is planned and no statistical inference will be made from the interim analysis results. Regardless of the interim analysis results, the study will be continued and completed. Maintaining stable background therapy until the end of the treatment period will prevent any independent confounding variables on the treatment effect of MEDI9929. Continuing stable background therapy through Week 64

will permit duration of response analysis after the last dose of MEDI9929 in order to determine the dose-regimen for future studies.

An ECG sub-study will be done in subgroup of subjects to confirm that MEDI9929 does not affect cardiac electrophysiological intervals. Additionally, flow cytometry will be performed at selected sites to evaluate intracellular cytokines in T cells by flow cytometry following *ex vivo* stimulation by phorbol myristate acetate.

Subjects will be in this study for approximately 1.3 years (69 weeks), which includes a screening/run-in period of up to approximately 5 weeks, a 52-week treatment period, and a 12-week post-treatment follow-up period. The last dose of investigational product will be administered at Week 50.

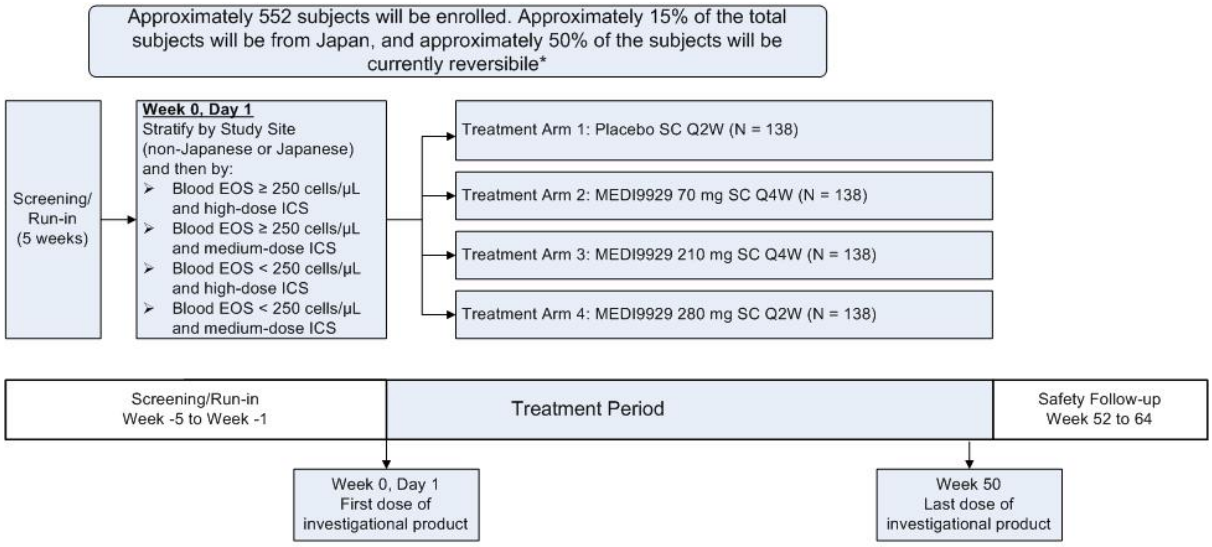

Figure 3.1.1-1 Study Flow Diagram

BD = bronchodilator; EOS = eosinophils; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; N = number of subjects per treatment group; Q2W = every 2 weeks; Q4W = every 4 weeks, SC = subcutaneous

Note: Every subject receives 3 injections of investigational product Q2W (subjects receiving MEDI9929 Q4W will receive placebo on alternate weeks in order to maintain the blind) in the study. All subjects will be on background asthma therapy of medium- or high-dose ICS and LABA with or without additional asthma controller medications (LTRA, LAMA, cromones, theophylline, and/or maintenance OCS) from screening through the follow-up period.

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

3.1.2 Treatment Regimen

Approximately 552 subjects will be randomized in a 1:1:1:1 ratio to receive one of 3 SC dose levels of MEDI9929 or SC placebo for 52 weeks as described in Table 3.1.2-1. All subjects will receive 3 injections (2 × 1.5 mL and 1 × 1.0 mL) Q2W in order to maintain the blinding of the different doses.

Table 3.1.2-1 Investigational Product Dose and Treatment Regimen

Treatment Arm	N	Dose	Treatment Regimen
1	138	Placebo	3 SC injections Q2W from Week 0, Day 1 to Week 50 • 1 × 1 mL placebo and 2 × 1.5 mL placebo
2	138	70 mg	3 SC injections Q4W from Week 0, Day 1 to Week 48 • 1 × 1 mL MEDI9929 and 2 × 1.5 mL placebo 3 SC injections Q4W from Week 2 to Week 50 • 1 × 1 mL placebo and 2 × 1.5 mL placebo
3	138	210 mg	3 SC injections Q4W from Week 0, Day 1 to Week 48 • 1 × 1 mL MEDI9929 and 2 × 1.5 mL (combining 1 mL MEDI9929 and 0.5 mL placebo in each syringe) 3 SC injections Q4W from Week 2 to Week 50 • 1 × 1 mL placebo and 2 × 1.5 mL placebo
4	138	280 mg	3 SC injections Q2W from Week 0, Day 1 to Week 50 • 1× 1 mL MEDI9929 and 2 × 1.5 mL MEDI9929

N = number of subjects in each treatment group; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous

3.2 Study Design and Dose Rationale

The study will be randomized, placebo-controlled, and double-blind to ensure a robust design and minimize bias. MEDI9929 would be expected to be administered over extended periods of time in order to demonstrate an adequate effect on the AER.

MEDI9929 is being developed as an asthma controller treatment that would be expected to be given over extended periods of time; therefore, a treatment period of 52 weeks is considered appropriate duration to ensure that adequate numbers of exacerbation events are observed during the study in order to determine the treatment effect on the primary endpoint.

There are few treatment options for patients whose asthma remains uncontrolled on high-dose ICS + LABA (GINA, 2012). The evidence base for oral add-on therapies (ie, oral corticosteroids, leukotriene inhibitors, and xanthenes) is extremely limited. Anti-IgE therapy (ie, omalizumab) may improve control in patients with severe asthma and IgE-mediated allergy to a perennial allergen; however the risk of combining biologic treatments is

unknown. Subjects in this study remain symptomatic despite maximal available therapy (medium- or high-dose ICS plus LABA, with or without additional asthma controller medications), as such, placebo is an appropriate comparator for this study.

3.2.1 Dose Rationale

Three dose levels of MEDI9929 will be evaluated in this dose-ranging study to explore the optimal dose and regimen of MEDI9929 for use in this patient population. The low (70 mg Q4W), medium (210 mg Q4W), and high (280 mg Q2W) dose levels of MEDI9929 were selected to provide minimum exposure overlap between treatment arms. There are no established PD markers available to directly determine the level of TSLP inhibition provided by the selected dose levels. Therefore, it is not feasible to significantly narrow the selected dose range.

The high-dose (280 mg Q2W) of MEDI9929 approximates the trough levels achieved in the inhaled allergen challenge study (Study 20101183) with 700 mg IV Q4W, which demonstrated improvement in physiologic measurements in subjects with mild atopic asthma. These dose regimens are also appropriate from a safety perspective as the predicted steady-state exposures are within the range of the exposures achieved in previous studies.

3.2.2 Rationale for Study Population

Subjects in this study will have inadequately controlled, severe asthma requiring therapy outlined in GINA Step 4 or Step 5. Severe asthma is asthma that requires high intensity treatment (eg, GINA Step 4 and Step 5) to maintain good control, or where good control is not achieved despite high intensity treatment (GINA, 2012). In this study, all subjects will receive stable background asthma therapy of medium- or high-dose ICS and LABA, with or without additional asthma controller medications (LTRA, LAMA, cromones, theophylline, and/or maintenance OCS) that is consistent with GINA Step 4 and Step 5. For this study, subjects are required to be on medium- or high-dose ICS/LABA for at least a year, have a history of at least 2 documented asthma exacerbation events or at least 1 severe asthma exacerbation resulting in hospitalization (admission to the hospital for at least 24 hours) within a year prior to entering the study, and continue to exhibit asthma symptoms consistent with partially controlled or uncontrolled asthma according to GINA guidelines (GINA, 2012, ie, inadequate control).This duration of asthma treatment requirement increases the likelihood that those subjects that have not been given adequate time for treatment to work and those that have been under-treated will be eliminated from participation in the study. This population also represents those with the greatest unmet medical need in this disease. Although treatment with omalizumab (anti-IgE, Xolair®) is consistent with GINA Step 5

treatment guidelines, subjects on omalizumab will be excluded from this study. The risks of combining omalizumab with MEDI9929 are unknown. Subjects on maintenance OCS, in addition to ICS and LABA are eligible to be enrolled in the study.

Subjects will be stratified by ICS dose level (medium or high) at randomization to ensure that at least 40% of subjects will be taking high-dose ICS, and these subjects will be dispersed across treatment groups. Subjects taking maintenance OCS will be automatically assigned to the high-dose stratum. A minimum of 40% of subjects is needed for subgroup analysis to see if there is a difference in treatment effect based upon ICS dose, and because currently only patients on high-dose ICS and/or maintenance OCS are eligible to receive biologic therapy in some countries.

The majority of scientific evidence regarding the role of TSLP in asthma is from nonclinical data, and suggests that after TSLP is released from airway epithelial cells or stromal cells, it activates mast cells, dendritic cells, and T cells to release Th2 cytokines (eg, IL-4/13/5). Recently published human data demonstrated a good correlation between tissue TSLP gene and protein expression, a Th2 gene signature score, and tissue eosinophils in severe asthma. Therefore, an anti-TSLP target therapy may be effective in asthmatic patients with Th2-type inflammation (Shikotra et al, 2012). This conjecture is supported by the impact of inhibiting TSLP with MEDI9929 on blood and sputum eosinophils and Th2/Th1 ratios in the inhaled allergen challenge study (Study 20101183) although only atopic, likely Th2-type, patients were studied.

Data from other studies suggest that TSLP may promote airway inflammation through Th2 independent pathways such as the crosstalk between airway smooth muscle and mast cells (Allakhverdi et al, 2009; Shikotra et al, 2012). TSLP can also promote induction of T cells to differentiate into Th-17-cytokine producing cells with a resultant increase in neutrophilic inflammation commonly seen in more severe asthma (Tanaka et al, 2009). These data and other emerging evidence suggest that blocking TSLP may serve to suppress multiple biologic pathways including but not limited to those involving Th2 cytokines (IL-4/13/5), so MEDI9929 may prove to have clinical efficacy in asthmatic patients with both Th2- and non-Th2-type inflammation.

In order for analyses of the subgroups to be possible, the study population will include subjects with both Th2 and non-Th2-type inflammation, and the primary stratification factor will be based upon a measure of Th2 inflammation (eosinophils). However, there is no universally accepted method of identifying Th2-type inflammation in asthma. Eosinophils and mast cells are primary inflammatory cells involved in Th2 inflammation. A number of

new asthma therapies under development have been directed against Th2 cytokines including IL-5 and IL-13. Lebrikizumab, an anti-IL-13 mAb identified two potential methods to identify Th2-type asthma (Corren et al, 2011). One method identified a "Th2 asthma" responder population with a combination of IgE and blood eosinophils (IgE > 100 IU/mL and blood eosinophil count ≥ 140 cells/μL; Corren et al, 2011). The other approach used serum periostin, a matricellular profibrotic protein released by epithelial cells in response to IL-13, which is highly correlated with eosinophilic airway inflammation (Jia et al, 2012), and has been used to identify a responder population in subjects with asthma (Corren et al, 2011). Classification of Th2-type inflammation by these methods is not as well established as using blood eosinophils, and they are more difficult to implement operationally into the study. Therapies directed at anti-IL-5 pathways have targeted eosinophilic asthma which was traditionally identified by sputum eosinophilia. This method is not suitable for clinical trials and measurement of blood eosinophils has been identified as a reasonable surrogate for eosinophilic asthma. Each of these methods identifies approximately 50% of severe asthmatics as having Th2-type inflammation in asthma. There is considerable, but not 100% overlap between these methods for identifying Th2-type inflammation in asthma.

In this study, subjects will be stratified by blood eosinophil count (≥ or < 250 cells/μL) as a surrogate measure of Th2-type inflammation. Using blood eosinophils is acceptable for large, global clinical studies because the test is widely available, reliable, and valid. The blood eosinophil count cutoff of 250 cells/μL was chosen based on the median blood eosinophil count observed in similar patient populations from 2 recently conducted asthma studies at MedImmune. A recent study evaluating the response of Th2-driven subpopulations of severe asthmatics to treatment with omalizumab demonstrated that a blood eosinophil cutoff of ≥ 260 cells/μL served to discriminate between those who responded to this therapy and those who did not (Hanania et al, 2013). The choice of a blood eosinophil cutoff of ≥ 250 cells/μL as a proxy for Th2-type asthma for this study is therefore reasonable, and will provide for a sufficient number of subjects with Th2-type and non-Th2-type asthma for a subgroup analysis and determination of efficacy in these populations.

Reversibility to beta agonists may also be a marker of aTh2 inflammatory process (Moore et al, 2010). Because of this possibility, and to ensure that the study does not enroll a predominantly non-reversible population, the protocol requires at least 50% of the study population to demonstrate current post-BD FEV_1 reversibility, defined as ≥ 12% and ≥ 200 mL improvement in FEV_1 on at least one of the 3 screening/run-in visits (Visit 1 [Week -5], Visit 2 [Week -4], or Visit 3 [Week -1]). Because of the complexity of having 3 strata in the interactive voice/web response system (IXRS), this protocol will not stratify by

current post-BD FEV_1 reversibility, but will require that at least 50% of the study population demonstrate current post-BD FEV_1 reversibility.

It is generally recommended that Japanese subjects be included in studies to identify inter-ethnic differences in the dose-response relationship early in clinical development. The target percentage of Japanese subjects for inclusion in this study is approximately 15% of the targeted enrollment of 552 subjects. Subgroup analysis for the Japanese population will be performed.

3.2.3 Rationale for Endpoints

MEDI9929 is being developed as a controller therapy for subjects with inadequately controlled, severe asthma with the aim to achieve and maintain asthma control for prolonged periods. The GINA guidelines (GINA, 2012) recommend that the assessment of asthma control should not only include the control of clinical manifestations (symptoms, sleep disturbance, limitation of daily activity, impaired lung function, and use of rescue medication) but also the control of expected future risk including the incidence of asthma exacerbations. The endpoints chosen for this study provide the opportunity to assess the impact of MEDI9929 on these different aspects of asthma control.

Asthma exacerbations are important because they constitute the greatest medical risk to patients, are a cause of anxiety to patients and their families, result in the greatest stress on healthcare providers, and generate the greatest cost to the health care systems (Lane et al, 2006). It is therefore important to establish whether the use of MEDI9929, in addition to GINA Step 4 or 5 standard of care, is associated with a reduction in the annual asthma exacerbation rate (see Section 4.3.1.1 for definition of asthma exacerbation) when compared to placebo in addition to GINA Step 4 or 5 standard of care. The rate of asthma exacerbations has therefore been selected as the primary efficacy variable. Additional measures associated with asthma exacerbations are also being examined to determine effect. These include hospitalizations related to asthma exacerbations (ie, severe asthma exacerbations), time to first asthma exacerbation, and the proportion of subjects with one or more asthma exacerbation/severe asthma exacerbation.

The secondary endpoints include other established measures of asthma control (eg, pulmonary function, asthma symptoms, and rescue asthma medication use) and quality of life, which together with the safety and tolerability of MEDI9929 will be critical in establishing the potential clinical utility of MEDI9929.

Additional secondary and exploratory endpoints in the study will help identify the optimal dose and dose regimen to be used in future studies, along with the subpopulation(s) that is likely to respond to treatment with MEDI9929. The asthma subpopulations include, but are not limited to: eosinophilic and non-eosinophilic; Th2 high/low (Corren et al, 2011); FE_{NO} high/low; periostin high/low; current post-BD FEV_1 reversibility; allergic and non-allergic; and markers of TSLP pathway activation (to be determined). A similar approach has been used in a recent study exploring the effect of omalizumab in subsets of asthmatics with and without evidence of Th2-type inflammation (Hanania et al, 2013).

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Approximately 552 subjects will be randomized in a 1:1:1:1 ratio to receive one of 3 doses of MEDI9929 or placebo. Approximately 138 subjects will be randomized to each treatment arm.

Subjects will be stratified as described in Section 3.1.1. The target enrollment for each stratification factor is as follows:

- Study sites (non-Japanese or Japanese) - Japanese population will account for approximately 15% of the targeted enrollment of 552 subjects.
- Blood eosinophil count - at least 50% of all subjects randomized will have blood eosinophil count ≥ 250 cells/μL.
- ICS dose level - at least 40% of all subjects randomized will be taking high-dose ICS and/or maintenance OCS.

In addition to the target enrollment for each stratification factor, at least 50% of subjects in the study will demonstrate current post-BD FEV_1 reversibility.

4.1.2 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1. Age 18 through 75, inclusive at the time of Visit 1 (Week -5).
2. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act [HIPAA] in the USA, European Union [EU] Data Privacy Directive in the EU) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations.

3. Body mass index between 18-40 kg/m^2, inclusive and weight ≥ 40 kg at Visit 1 (Week -5).
4. Documented physician-diagnosed asthma for at least 12 months prior to Visit 1 (Week -5) and post-BD reversibility of FEV_1 ≥ 12% and ≥ 200 mL during screening. Documented history of post-BD FEV_1reversibility in the past 12 months will be accepted in place of reversibility during screening.
5. For subjects 65 years or older at Visit 1 (Week -5) a chest x-ray (CXR) taken during the screening period or a CXR or chest computed tomography scan within 12 months prior to Visit 1 (Week -5) that, according to the investigator, is normal for an asthmatic subject and excludes significant alternative respiratory disease is required.
6. Subjects must have received a physician-prescribed asthma controller regimen with medium- or high-dose ICS plus LABA for at least 6 months prior to Visit 1 (Week -5), and the dose of ICS must be stable for at least 15 days prior to Visit 1 (Week -5) and throughout the screening/run-in period.
   - To be classified as being on high-dose ICS, the subjects will be on a total daily dose of > 500 µg fluticasone dry powder inhaler (DPI), or a total daily dose of > 440 µg fluticasone metered dose inhaler (MDI) or equivalent.
   - To be classified as being on medium-dose ICS, the subjects will be on a total daily dose (sum of all ICS) of 250 to 500 µg fluticasone DPI or a total daily dose of 220 to 440 µg fluticasone MDI or equivalent.
   - Equivalent ICS doses will be based upon the GINA guidelines (GINA, 2012), shown in Appendix 5.
7. If on asthma controller medications in addition to ICS plus LABA, the dose of the other asthma controller medications (leukotriene receptor inhibitors, theophylline, secondary ICS, LAMA, cromones, or maintenance oral prednisone or equivalent up to a maximum of 10 mg daily or 20 mg every other day for the maintenance treatment of asthma) must be stable for at least 15 days prior to Visit 1 (Week -5).
8. Subjects must have a morning pre-BD FEV_1 value of ≥ 40% and ≤ 80%, predicted at 2 Screening Visits. The first time must be at either Visit 1 (Week -5) or Visit 2 (Week -4), and the second time must be at Visit 3 (Week -1).
9. Subjects must have an ACQ-6 score of ≥ 1.5 twice during screening. The first time must be at Visit 1 (Week -5). The second time may be at either Week -2 (taken from home recording on the electronic patient-reported outcome [ePRO] device) or at Visit 3 (Week -1).
10. At Visit 4 (Week 0, Day 1), subjects must have at least one of the following over the previous 7 days from the ePRO device:
    - > 2 days with a daytime or nighttime symptoms score ≥ 1 (Asthma Daily Diary); or
    - ≥ 1 awakening due to asthma requiring rescue medication use; or
    - Rescue/reliever short-acting β2 agonist (SABA) use > 2 days.
11. Subjects must have a documented history of at least 2 asthma exacerbation events OR at least 1 severe asthma exacerbation resulting in hospitalization (admission to the hospital for at least 24 hours) within the 12 months prior to Visit 1 (Week -5). To qualify as an asthma exacerbation event, administration of a burst of systemic corticosteroids for at

least 3 consecutive days must have been required for the treatment of the asthma exacerbation, or the asthma exacerbation resulted in an emergency department (ED) visit which required systemic corticosteroids for at least 3 consecutive days or hospitalization. For subjects receiving maintenance OCS, a temporary doubling of the stable existing maintenance dose for at least 3 days qualifies.

12. If on allergen-specific immunotherapy subjects must be on a maintenance dose and schedule for at least 2 months prior to Visit 1 (Week -5).
13. Subjects must meet the all of following criteria at Visit 4 (Week 0, Day 1) prior to randomization:
    - Subjects must demonstrate acceptable inhaler, peak flow meter, and spirometry techniques during screening/run-in period (from Visit 2 to Visit 4).
    - Subjects must demonstrate ≥ 70% compliance with usual asthma controller ICS/LABA during the screening/run-in period (from Visit 2 to Visit 4) based on the Asthma Daily Diary.
    - Subjects must demonstrate ≥ 80% compliance with required use of the ePRO device; 80% compliance is defined as completing the Asthma Daily Diary for any 8 mornings and any 8 evenings in the previous 10 days of the screening/run-in period.
14. Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception from the time informed consent is obtained and must agree to continue using such precautions through Week 64 of the study; cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.
    - Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
    - A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table 4.1.2-1.

Table 4.1.2-1 Highly Effective Methods of Contraception

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

[a] This is also considered a hormonal method.

4.1.3 Exclusion Criteria

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

1. Diagnosis of vocal cord dysfunction, reactive airways dysfunction syndrome, hyperventilation and panic attacks, or other mimics of asthma.
2. An established diagnosis of occupational asthma.
3. Current smokers or subjects with a smoking history of ≥ 10 pack years (number of pack years = number of cigarettes per day/20 × number of years smoked). Former smokers with < 10 pack years must have stopped for at least 6 months to be eligible.
4. Previous medical history or evidence of an uncontrolled intercurrent illness that in the opinion of the investigator and/or medical monitor may compromise the safety of the subject in the study or interfere with evaluation of the investigational product or reduce the subject's ability to participate in the study. Subjects with well-controlled comorbid disease (eg, hypertension, hyperlipidemia, gastroesophageal reflux disease) on a stable treatment regimen for 15 days prior to Visit 1 (Week -5) are eligible.
5. Any concomitant respiratory disease that in the opinion of the investigator and/or medical monitor will interfere with the evaluation of the investigational product or interpretation of subject safety or study results (eg, chronic obstructive pulmonary disease, cystic fibrosis, pulmonary fibrosis, bronchiectasis, allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome).
6. Any clinically relevant abnormal findings in hematology, clinical chemistry, or urinalysis (laboratory results from Visit 1 [Week -5] and Visit 3 [Week -1]), physical examination, vital signs during the screening/run-in period, which in the opinion of the investigator, may put the subject at risk because of his/her participation in the study, or may influence the results of the study, or the subject's ability to participate in the study.
7. Evidence of active liver disease, including jaundice or aspartate transaminase, alanine transaminase, or alkaline phosphatase greater than twice the upper limit of normal (laboratory results from Visit 1 [Week -5] and Visit 3 [Week -1]).
8. History of cancer:
    - Subjects who have had basal cell carcinoma or in situ carcinoma of the cervix are eligible to participate in the study provided that curative therapy was completed at least 12 months prior to Visit 1 (Week -5).
    - Subjects who have had other malignancies are eligible provided that curative therapy was completed at least 5 years prior to Visit 1 (Week -5).
9. Acute upper or lower respiratory infections requiring antibiotics or antiviral medications within 15 days prior to Visit 1 (Week -5), during the screening/run-in period, or at Visit 4 (Week 0, Day 1).
10. Evidence of a clinically significant infection or receiving treatment with antibiotics or antiviral medications at Visit 4 (Week 0, Day 1).
11. A helminth parasitic infection diagnosed within 24 weeks of Visit 1 (Week -5) that has not been treated, or has not responded to standard of care therapy.

12. Known history of active tuberculosis (TB) or a positive QuantiFERON®-tuberculosis Gold (QFT-G) test for TB during screening. Subjects with a positive or indeterminate QFT-G result may be enrolled if they have ALL of the following:
    - No symptoms of TB: productive, prolonged cough (> 3 weeks); coughing up blood; fever; night sweats; unexplained appetite loss; unintentional weight loss.
    - No known exposure to a case of active TB after most recent prophylaxis (prophylaxis required only if positive).
    - No evidence of active TB on chest radiograph within 3 months prior to the first dose of investigational product.

Subjects with an indeterminate QFT-G result will have repeat QFT-G testing during the study (Weeks 12, 28, 40, and 52).

13. Positive hepatitis B surface antigen, or hepatitis C virus antibody serology at screening, or a positive medical history for hepatitis B or C. Subjects with a history of hepatitis B vaccination without history of hepatitis B are allowed to enroll.
14. A positive human immunodeficiency virus (HIV) test at screening or subject taking antiretroviral medications, as determined by medical history and/or subject's verbal report.
15. History of sensitivity to any component of the investigational product formulation or a history of drug or other allergy that, in the opinion of the investigator or medical monitor contraindicates their participation.
16. History of anaphylaxis to any biologic therapy.
17. History of documented immune complex disease (Type III hypersensitivity reactions) to mAb administration.
18. History of any known primary immunodeficiency disorder excluding asymptomatic selective immunoglobulin A or IgG subclass deficiency.
19. Systemic corticosteroid burst including taper within 15 days prior to Visit 1 (Week -5) or during the screening/run-in period.
20. Use of 5-lipoxygenase inhibitors (eg, zileuton) within 15 days prior to Visit 1 (Week -5).
21. Use of immunosuppressive medication (eg, methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid, or any experimental anti-inflammatory therapy) within 3 months prior to Visit 1 (Week -5). Chronic oral prednisone or equivalent up to a maximum of 10 mg daily or 20 mg every other day for the maintenance treatment of asthma is permitted.
22. Receipt of any of the following within 30 days prior to Visit 1 (Week -5)
    - Immunoglobulin or blood products, or
23. Receipt of any investigational nonbiologic agent within 30 days or 5 half-lives prior Visit 1 (Week -5), whichever is longer.
24. Receipt of any marketed (including omalizumab) or investigational biologic agent within 4 months or 5 half-lives prior to Visit 1 (Week -5), whichever is longer.
25. Pregnant, breastfeeding or lactating females
26. History of chronic alcohol or drug abuse within 12 months prior to Visit 1 (Week -5).

27. Planned surgical procedures requiring general anesthesia or in-patient status for > 1 day during the conduct of the study.
28. Unwillingness or inability to follow the procedures outlined in the protocol to Week 64.
29. Concurrent enrollment in another clinical study involving an investigational treatment.
30. Receipt of any oral or ophthalmic β-adrenergic antagonists (eg, propranolol) within 15 days prior to Visit 1 (Week -5).
31. Receipt of the Th2 cytokine inhibitor suplatast within 15 days prior to Visit 1 (Week-5).
32. Receipt of any live or attenuated vaccines within 15 days prior to Visit 1 (Week -5).

4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by an IXRS, and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

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

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not be randomized or receive investigational product.

4.1.5 Withdrawal from the Study

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

4.1.6 Discontinuation of Investigational Product

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 from further treatment with investigational product or lost to follow-up.
2. An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing.
3. Subject is determined (after randomization) to have met one or more of the exclusion criteria related to safety prior to being randomized in the study.
4. Pregnancy (see Section 5.6.3).

Subjects who prematurely discontinue receiving investigational product will be identified as having permanently discontinued treatment regardless of the reason (eg, withdrawal of consent, due to an AE, other).

When feasible, compliant subjects who are discontinued from receiving the investigational product should be encouraged to undergo all study related visits/procedures through Week 64 (Visit 32), including safety follow-up, in order to support the final efficacy and safety analyses for MEDI9929.

Subjects who are prematurely discontinued from receiving investigational product are encouraged to undergo all study-related visits/procedures through Week 64. If a subject is not willing to continue to participate in the study, the subject should return to the study site and complete procedures according to Visit 30 (Early Discontinuation Visit [EDV]) and return 12 weeks after the EDV for safety follow-up and protocol-specified assessments according to Visit 32 (Safety Follow-up Visit [SFV]). Study procedures including PRO assessments will continue until the SFV.

The EDV will be the final study visit, and the SFV will not be conducted, in the following circumstances.

- Consent is withdrawn specifically from further study participation (Section 4.1.5).
- The subject is lost to follow-up.
- The subject starts an alternative treatment (eg, one of the prohibited medications).
- The subject is enrolled in another clinical study.

4.1.7 Replacement of Subjects

Subjects in this study will not be replaced.

4.1.8 Withdrawal of Informed Consent for Data or Samples

Biological Samples Obtained for the Main Study

Study data are protected by the use of a SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any data or samples collected prior to that time may still be given to and used by the sponsor, but no new data or samples will be collected unless specifically required to monitor safety of the subject.

Samples Obtained for Genetic Research (DNA)

Samples obtained for genetic research are protected by the use of a SID number, which is a number specific to the subject. If the subject consents to have his/her samples used for genetic research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s), including any specimens of extracted DNA will be stored by the sponsor with similar sample(s) from other subjects at a secure central laboratory. The subject's sample(s) will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study sample(s) to be used for genetic research, the sample(s) will be destroyed by the sponsor.

If consent is withdrawn after sample(s) have been taken, but before the subject's samples are sent to the sponsor for genetic research, the investigator will arrange to have the sample(s) destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the sponsor for genetic research, the sponsor and the investigator will ensure that these sample(s) are destroyed. However, if the subject's sample(s) have already been used for research, the sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

4.2 Schedule of Study Procedures

4.2.1 Enrollment/Screening Period

Table 4.2.1-1 shows all procedures to be conducted at the screening/run-in visits. Assessments should be performed in the order shown in the table. The ECG assessments will be performed prior to any blood draws, FE_{NO}, spirometry, and administration of investigational product. In addition, FE_{NO} will be performed prior to spirometry.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations.

Rescreening

If a subject is to be rescreened, they will be considered a screen failure and will be rescreened with a new SID. All Visit 1 (Week -5) assessments are to be performed, and written informed consent should be obtained again. **Rescreening is generally only permitted once**, when there is a reasonable expectation that the subject will become eligible for the study. Permission to rescreen > 1 time may be granted in the presence of extenuating circumstances and only with prior approval of the medical monitor. Rescreening is not permitted if the reason for screen failure is Inclusion Criterion No. 9 (ACQ eligibility criterion; Section 4.1.2).

Table 4.2.1-1 Schedule of Screening Procedures

Study Period	**Screening Run-in Period**		
Visit Number	**1**	**2**	**3**
Study Week	**-5**	**-4**	**-1**
Procedure/Visit Window	**+ 2 D**	**± 2 D**	**± 2 D** [a]
Written informed consent/consent for DNA/assignment of SID number	X		
ePRO device training [b]	X	X	
Complete ACQ-6 at site in ePRO device	X	X	X
Home peak flow monitor training and distribution		X	
Distribute ePRO device		X	
Check compliance with PRO assessments			X
Check compliance and technique with home peak flow meter			X
Medical and asthma history	X		
Concomitant medications	X	X	X
Assessment of AEs/SAEs	X	X	X
Assessment of asthma exacerbations	X	X	X
Physical examination, height and weight	X		
Vital signs	X	X	X
ECG [c]	X		
Chest x-ray (if required) [d]	X		
Serum chemistry	X		X

Table 4.2.1-1 Schedule of Screening Procedures

Study Period	Screening Run-in Period		
Visit Number	**1**	**2**	**3**
Study Week	**-5**	**-4**	**-1**
Procedure/Visit Window	**+ 2 D**	**± 2 D**	**± 2 D [a]**
Hematology	X		X
CBC with differentials at local laboratory [e]	X		X
Total serum IgE			X
Urinalysis	X		X
Pregnancy test, serum (females only [f])	X		
Hepatitis B, C; HIV-1, HIV-2	X		
QFT-G test	X		
FE_{NO}	X	X	X
Spirometry (pre-BD)	X	X	X
Spirometry (post-BD)	X	X	X
Verify eligibility criteria	X	X	X

ACQ -6 = Asthma Control Questionnaire, omitting FEV_1; ACQ -6 = Asthma Control Questionnaire, omitting FEV_1; AQLQ(S)+12 = Asthma Quality of Life Questionnaire (Standardised); AE = adverse event; CBC = complete blood count; D = Day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D-5L = European Quality of Life - 5 Dimensions 5 Level Version; ePRO = electronic patient-reported outcome; FE_{NO} = fraction of exhaled nitric oxide; FEV_1 = forced expiratory volume in one second; HIV = human immunodeficiency virus; IgE = immunoglobulin E; post-BD = post-bronchodilator; pre-BD = pre-bronchodilator; PRO = patient reported outcome; QFT-G = QuantiFERON® -tuberculosis Gold; SAE = serious adverse event; SID = subject identification; TB = tuberculosis; WPAI+CIQ = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions

[a] There must be a minimum of 5 days between Visit 3 and Visit 4

[b] The PRO assessments include Asthma Daily Diary, ACQ-6, AQLQ(S)+12, EQ-5D-5L, WPAI+CIQ. The assessment schedules are programmed into the ePRO device. Subjects will be triggered to complete the appropriate questionnaires/assessments at the appropriate intervals (eg, daily, weekly, biweekly)

[c] The ECG is to be completed in triplicate until site is notified by sponsor that ECG sub-study is complete

[d] The chest x-ray may be done at another visit during the screening/run-in period if necessary, as long as results have been reviewed prior to randomization

[e] The CBC samples should be analyzed as quickly as possible, preferably within 12 hours of sample collection

[f] The serum pregnancy test will be required of all females in the study regardless of childbearing potential

4.2.2 Treatment Period

Table 4.2.2-1 and Table 4.2.2-2 show all procedures to be conducted during the treatment period. Each visit during the treatment period must be scheduled within the visit window (ie, ± 3 days). **If a visit does not occur during the visit window, then the subject may not receive the investigational product and this will be considered a missed dose.** The reason for the missed dose must be documented and the next dose of investigational product should not be administered until the next visit.

Assessments should be performed in the order shown in the table. The ECG assessments will be performed prior to any blood draws, FE_{NO}, spirometry, and administration of investigational product. In addition, FE_{NO} will be performed prior to spirometry.

Table 4.2.2-1 Schedule of Treatment Period Study Procedures Week 0 to Week 24

Study Period	Treatment Period												
Visit Number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Study Week	**0 (Day 1)**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Procedure/Visit Window	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**
Verify eligibility criteria	X												
Check compliance with PRO assessments [a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Check compliance and technique with home peak flow meter	X	X	X	X	X	X	X	X	X	X	X	X	X
PRO assessments at site	X												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs and SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of asthma exacerbations	X	X	X	X	X	X	X	X	X	X	X	X	X
HRU	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, including weight	X												
Vital signs [b]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG [c]	X						X				X		
Serum chemistry	X		X				X				X		
Hematology	X		X				X				X		
Urinalysis	X		X				X				X		
Urine pregnancy test (females of childbearing potential only)	X	X	X	X	X	X	X	X	X	X	X	X	X
QFT-G test [d]							X						
IgE FEIA	X												
Total serum IgE	X		X				X				X		

Table 4.2.2-1 Schedule of Treatment Period Study Procedures Week 0 to Week 24

Study Period	**Treatment Period**												
Visit Number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Study Week	**0 (Day 1)**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Procedure/Visit Window	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**
Serum for PK	X		X				X				X		
Serum for ADA	X		X				X				X		
Serum for biomarker analysis	X		X				X				X		
Whole blood for flow cytometry (selected sites)	X						X						
Blood sample for DNA (optional)	X												
FE_{NO}	X		X		X		X				X		
Spirometry (pre-BD)	X		X		X		X				X		
Spirometry (post-BD)	X												
Randomize	X												
Investigational product administration [e]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

ACQ -6 = Asthma Control Questionnaire, omitting FEV_1; ADA = anti-drug antibodies; AE = adverse event; AQLQ(S)+12 = Asthma Quality of Life Questionnaire (Standardised); D = Day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ePRO = electronic patient reported outcome; EQ-5D-5L = European Quality of Life - 5 Dimensions 5 Level Version; FEIA = fluorescence enzyme immunoassay; FE_{NO} = fraction of exhaled nitric oxide; FEV_1 = forced expiratory volume in one second; HRU = healthcare resource utilization; IgE = immunoglobulin E; PK = pharmacokinetic(s); post-BD = post-bronchodilator; pre-BD = pre-bronchodilator; PRO = patient reported outcome; QFT-G = QuantiFERON® -tuberculosis Gold; SAE = serious adverse event; WPAI+CIQ = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions

[a] The PRO assessments include Asthma Daily Diary, home peak flow, ACQ-6, AQLQ(S)+12, EQ-5D-5L, WPAI+CIQ. The assessment schedules are programmed into the ePRO device. Subjects will be triggered to complete the appropriate questionnaires/assessments at the appropriate intervals (eg, daily, weekly, biweekly)

[b] Vital signs will be done prior to investigational product administration, 60 and 120 minutes (± 5 minutes) after the first 5 doses of investigational product are administered, and 60 minutes (± 5 minutes) after the sixth and subsequent doses of investigational product are administered. If the subject is not stable, vital signs should be monitored at least hourly until the subject is discharged from the study center

Table 4.2.2-1 Schedule of Treatment Period Study Procedures Week 0 to Week 24

Study Period	Treatment Period												
Visit Number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Study Week	**0 (Day 1)**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Procedure/Visit Window	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**

[c] The ECG is completed in triplicate until site notified by sponsor that the ECG sub-study is complete

[d] Only subjects with an indeterminate QFT-G result at screening

[e] There must be ≥ 7 days between doses.

Table 4.2.2-2 Schedule of Treatment Period Study Procedures - Week 26 to Week 52

Study Period	Treatment Period													
Visit Number	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**EDV30**
Study Week	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**
Procedure/Visit Window	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**
Check compliance with PRO assessments [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Check compliance and technique with home peak flow meter	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
Assessment of AEs and SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of asthma exacerbations	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HRU	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, including weight		X												X
Vital signs [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG [c]		X						X						X
Serum chemistry		X						X						X
Hematology		X						X						X
Urinalysis		X						X						X
Urine pregnancy test (females of childbearing potential only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QFT-G test [d]		X						X						X
Total serum IgE		X						X						X
Serum for PK		X						X						X
Serum for ADA		X						X						X
Serum for biomarker analysis		X						X						X

Table 4.2.2-2 Schedule of Treatment Period Study Procedures - Week 26 to Week 52

Study Period	Treatment Period													
Visit Number	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**EDV30**
Study Week	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**
Procedure/Visit Window	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**
Whole blood for flow cytometry (selected sites)		X												X
FE_{NO}		X						X						X
Spirometry (pre-BD)		X						X						X
Spirometry (post-BD)		X												X
Investigational product administration [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	

ACQ -6 = Asthma Control Questionnaire, omitting FEV_1 ADA = anti-drug antibodies; AE = adverse event; AQLQ(S)+12 = Asthma Quality of Life Questionnaire (Standardised); D = day; ECG = electrocardiogram; EDV = early discontinuation visit; ePRO = electronic patient reported outcome; EQ-5D-5L = European Quality of Life - 5 Dimensions 5 Level Version; FE_{NO} = fraction of exhaled nitric oxide; HRU = healthcare resource utilization; IgE = immunoglobulin E; PK = pharmacokinetic(s); post-BD = post-bronchodilator; pre-BD = pre-bronchodilator; PRO = patient reported outcome; QFT-G = QuantiFERON® -tuberculosis Gold; SAE = serious adverse event WPAI+CIQ = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions

[a] The PRO assessments include Asthma Daily Diary, home peak flow, ACQ-6, AQLQ(S)+12, EQ-5D-5L, WPAI+CIQ. The assessment schedules are programmed into the ePRO device. Subjects will be triggered to complete the appropriate questionnaires/assessments at the appropriate intervals (eg, daily, weekly, biweekly)

[b] Vital signs will be done prior to investigational product administration, 60 and 120 minutes (± 5 minutes) after the first 5 doses of investigational product are administered, and 60 minutes (± 5 minutes) after the sixth and subsequent doses of investigational product are administered. If the subject is not stable, vital signs should be monitored at least hourly until the subject is discharged from the study center

[c] The ECG completed in triplicate until site notified by sponsor that ECG sub-study is complete

[d] Only subjects with an indeterminate QFT-G result at screening

[e] There must be ≥ 7 days between doses.

4.2.3 Follow-up Period

Table 4.2.3-1 shows all procedures to be conducted during the follow-up period. Assessments should be performed in the order shown in the table. Specifically, the ECG assessments will be performed prior to blood drawing, FE_{NO}, and spirometry, and FE_{NO} specifically will be performed prior to spirometry.

Table 4.2.3-1 Schedule of Follow-up Procedures

Study Period	Follow-up Period	
Visit Number	**31**	**SFV/ 32**
Study Week	**58**	**64**
Procedure/Visit Window	**± 7 D**	**± 7 D**
Check compliance with PRO assessments [a]	X	X
Check compliance and technique with home peak flow meter	X	X
Concomitant medications	X	X
Assessment of AEs and SAEs	X	X
Assessment of asthma exacerbations	X	X
HRU	X	X
Physical examination, including weight		X
Vital signs	X	X
ECG [b]		X
Serum chemistry		X
Hematology		X
Urinalysis		X
Urine pregnancy test (females of childbearing potential only)		X
Total serum IgE		X
Serum for PK		X
Serum for ADA		X
Serum for biomarker analysis		X
Whole blood for flow cytometry (at selected sites)		X
FE_{NO}	X	X
Spirometry (pre-BD)	X	X
Spirometry (post-BD)		X

ACQ -6 = Asthma Control Questionnaire, omitting FEV_1 ADA = anti-drug antibodies; AE = adverse event; AQLQ(S)+12 = Asthma Quality of Life Questionnaire (Standardised); D = day; ECG = electrocardiogram; ePRO = electronic patient reported outcome; EQ-5D-5L = European Quality of Life - 5 Dimensions 5 Level Version; FE_{NO} = fraction of exhaled nitric oxide; FEV_1 = forced expiratory volume in one second; HRU = healthcare resource utilization; IgE = immunoglobulin E; PK = pharmacokinetic(s); post-BD = post-bronchodilator; pre-BD = pre-bronchodilator; PRO= patient reported outcome; SAE = serious adverse event; SFV = safety follow-up visit; WPAI+CIQ = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions

Table 4.2.3-1 Schedule of Follow-up Procedures

Study Period	Follow-up Period	
Visit Number	**31**	**SFV/ 32**
Study Week	**58**	**64**
Procedure/Visit Window	**± 7 D**	**± 7 D**

[a] The PRO assessments include Asthma Daily Diary, home peak flow, ACQ-6, AQLQ(S)+12, EQ-5D-5L, WPAI+CIQ. The assessment schedules are programmed into the ePRO device. Subjects will be triggered to complete the appropriate questionnaires/assessments at the appropriate intervals (eg, daily, weekly, biweekly)

[b] Completed in triplicate until site notified by sponsor that sub-study is complete

Order of Assessments

The ***recommended*** order of assessments in this study is as follows (not all assessments are completed at each study visit):

1. Check subject compliance with patient reported outcome (PRO) assessments
2. PRO assessments completed at site (ACQ-6 on Visit 1 [Week -5]; and possibly at Visit 3 [Week -1] if subject did not complete at home), and all other PROs at Visit 4 [Week 0, Day 1])
3. Update concomitant medications
4. Assess for AEs and serious adverse events (SAEs)
5. Assessment of asthma exacerbations
6. Assess HRU
7. Perform physical examination and weight
8. Take vital signs
9. Perform ECG. See prohibited medication list in Table 4.3.3.4-1. The medication restriction is waived for the screening ECG at Visit 1 (Week -5). The ECG assessments will be performed at the same time of day as the screening ECG, and prior to blood drawing, FE_{NO}, spirometry, and administration of investigational product.
10. Collect blood samples and urine
11. Complete dipstick pregnancy test and make sure it is negative
12. Perform FE_{NO} after ensuring that no food or drink has been consumed in the previous hour
13. Perform spirometry (pre- and post-BD). See prohibited medication list in Table 4.3.1.3-1. If a subject has taken these medications within the prohibited timeframe, the spirometry testing should be rescheduled. Spirometry testing must also be performed in the morning between 0600 and 1200 according to the schedule of study procedures. After the first screening spirometry (Visit 1 [Week -5]), every effort should be made to conduct spirometry testing at the same time that the first spirometry testing was done

14. Administer investigational product
15. Take vital signs 60 and 120 minutes (± 5 minutes) after the first 5 doses of investigational product are administered, and 60 minutes (± 5 minutes) after the sixth and subsequent doses of investigational product are administered. If the subject is not stable, vital signs should be monitored at least hourly until the subject is discharged from the study center

4.3 Description of Study Procedures

4.3.1 Efficacy

4.3.1.1 Assessment of Asthma Exacerbations

For the purpose of the protocol, an asthma exacerbation will be defined as a worsening of asthma that leads to any of the following:

- Use of systemic corticosteroids for at least 3 days.
  - A single depo-injectable dose of corticosteroids is considered equivalent to a 3-day course of systemic corticosteroids.
  - For subjects receiving maintenance OCS, a temporary doubling of the maintenance dose for at least 3 days qualifies.
- An ED visit due to asthma that required systemic corticosteroids (as per above).
- An inpatient hospitalization due to asthma.

Subjects may receive up to 7 days treatment with systemic corticosteroids for an asthma exacerbation and must return to their previous stable asthma treatment regimen at that time. Although a single depo-injection of intra-muscular corticosteroids is considered equivalent to a course of corticosteroids, this route of administration is discouraged and should not be administered by the investigator or designee.

Worsening of asthma is defined as new or increased symptoms and/or signs (examination or lung function) that can be either concerning to the subject (subject-driven) or related to an Asthma Daily Diary alert (diary-driven) via the ePRO device. The ePRO device will be programmed to alert both the subject and study center when certain pre-specified (objective) asthma-worsening thresholds are crossed including:

- Decrease in morning peak flow ≥ 30% on at least 2 of 3 successive days compared with baseline (last 7 days of run-in), and/or
- A ≥ 50% increase in rescue medication (minimum increase of 2 or more puffs, or one new or additional nebulized β2 agonist) on at least 2 of 3 successive days compared with the average use for the previous week, and/or

- Nocturnal awakening due to asthma requiring rescue medication use for at least 2 of 3 successive nights, and/or
- An increase in total asthma symptom score (the sum of daytime [evening assessment] and nighttime [morning assessment]) of at least 2 units above the screening/run-in period average (last 10 days of screening/run-in), or the highest possible score (daily score of 6), on at least 2 of 3 successive days

If an exacerbation event is not associated with deterioration in at least one of the pre-specified objective measurements (eg, exacerbation event is subject-driven), the investigator will indicate on the electronic case report form (eCRF) any other objective measures that were used in their decision to classify this asthma worsening event as an asthma exacerbation.

Events that the investigator believes are exacerbations, but are not supported by any specified objective assessment in the eCRF will be reviewed by an independent external adjudication committee (see Section 4.3.1.1 below) to determine if they are a medically valid asthma exacerbation.

An asthma exacerbation that occurs within ≤ 7 days after the last dose of systemic steroids (oral, intramuscular, IV) prescribed for a prior asthma exacerbation, will be counted as the same asthma exacerbation event.

Subjects who have asthma exacerbations during the study may continue to receive investigational product if the investigator judges that it is medically appropriate for the subject to do so.

Reasonable attempts should be made by the investigator to bring the subject into the study center for evaluation of an asthma diary-driven alert or subject-driven asthma worsening, particularly when it results in additional treatment being prescribed. Note that adjustment of regular background asthma controller medication during the treatment period should be avoided unless deemed medically necessary by the investigator. Study center evaluations for asthma worsening may occur as an unscheduled visit or as part of an ordinary center visit if the worsening happens to be coincident with a scheduled visit window. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study center (eg, by the primary care healthcare provider or at an ED/hospital) and details entered into the exacerbation eCRF (EXACA) in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the appropriate module of the eCRF.

External Adjudication Committee

The purpose and remit of the independent external adjudication committee is to perform a periodic blinded review of all of the clinical, laboratory, imaging, and AE data available for asthma exacerbation events that are not supported by objective measures of asthma worsening as specified in the eCRF. The external adjudication committee is comprised of 3 voting members who will remain blinded to treatment assignment throughout the study. The committee does not include any investigators in this clinical study. Voting members are physicians with experience in respiratory diseases and in the diagnosis and management of asthma. Specific details about the committee will be included in an external adjudication committee charter.

4.3.1.2 Fraction of Exhaled Nitric Oxide

Airway inflammation will be evaluated using a standardized single-breath FE_{NO} (American Thoracic Society; ATS, 2005) test. Since spirometry can potentially impact the nitric oxide measurement, the FE_{NO} test needs be completed prior to spirometry. **In addition, subjects should not eat or drink 1 hour prior to having the FE_{NO}**, as this may affect the results.

The subject should be sitting during FE_{NO} testing; however, if the subject is unable to sit, then standing is acceptable. The FE_{NO} testing should be completed in the same manner (ie, sitting or standing) at every study visit. Subjects are to inhale to total lung capacity through the NIOX MINO® Airway Inflammation Monitor and then exhale for 10 seconds at 50 mL/sec (assisted by visual and auditory cues). The value obtained will be recorded and the process repeated for a total of 2 measurements. The 2 measurements will be printed to serve as a source document. The 2 FE_{NO} values will be entered into the eCRF.

NIOX MINO sensors will be replaced as recommended by the manufacturer.

4.3.1.3 Spirometry

Spirometry will be performed at study sites by the investigator or qualified designee on equipment provided by a central vendor according to ATS/European Respiratory Society (ERS) guidelines (Miller et al, 2005).

Spirometry testing must be performed in the morning between 0600 and 1200 according to the schedule of study procedures. After first screening spirometry (Visit 1 [Week -5]), every effort should be made to conduct spirometry testing at the same time as the screening

spirometry was completed. On treatment days, spirometry testing will be performed before administration of investigational product.

Subjects will be required to refrain from strenuous exercise for 30 minutes prior to spirometry testing and to withhold the medications listed in Table 4.3.1.3-1 prior to spirometry testing**. If a subject has taken these medications within the prohibited timeframe, the spirometry testing should be rescheduled**.

Table 4.3.1.3-1 Prohibited Medications and Minimum Time Intervals Prior to Spirometry Testing

Concomitant Medication	Minimum Time Interval from Last Medication Dose to Spirometry Testing
Short-acting bronchodilators (eg, SABA [albuterol/salbutamol]), short acting anti-cholinergics (eg, ipratropium)	6 hours
Long-acting bronchodilators (eg, LABA, LAMA)	12 hours

LABA = long-acting β2 agonist; LAMA = long-acting anti-muscarinics; SABA = short-acting β2 agonist

The subject should wear comfortable clothing which does not restrict the chest or abdomen. The subject should rest for at least 15 minutes prior to the test.

The subject 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 2 best efforts that meet ATS/ERS acceptability and reproducibility criteria will be recorded. The best efforts will be based on the highest FEV_1. The maximum FEV_1 of the 2 best efforts will be used for the analysis. Both the absolute measurement (for FEV_1 and FVC) and the percentage of predicted normal value will be recorded using appropriate reference values. The highest FVC will also be reported regardless of the effort in which it occurred (even if the effort did not result in the highest FEV_1). Nose clips will be used for office spirometry.

Post-bronchodilator Assessment

Post-BD spirometry testing will be assessed at specified visits after the subject has performed pre-BD spirometry. Maximal bronchodilation will be induced using a SABA such as albuterol (90 µg metered dose) or salbutamol (100 µg metered dose) or equivalent with a spacer device for a maximum of 8 total puffs (Sorkness et al, 2008). **The same number of**

puffs (ie, 4, 6, or 8 puffs) and post-BD maneuvers used at baseline (Visit 4, Week 0, Day 1) to identify the maximal post-BD FEV_1 measurement, must be used each time post-BD spirometry testing is performed. Post-BD spirometry assessment is displayed in Figure 4.3.1.3-1 and outlined below.

1. Pre-BD spirometry assessments will be completed as described above
2. After an unforced and complete expiration, one metered puff of SABA will be inhaled in one breath to total lung capacity from a spacer device
3. Breath is then held for 5-10 seconds before the subject exhales
4. Repeat 3 more times using this method at 30-second intervals (for a total of 4 separate puffs of SABA)
5. Wait 15-20 minutes
6. First post-BD spirometry will be performed and post-BD FEV_1 measurement will be obtained
7. Administer 2 additional separate puffs of SABA
8. Wait 15-20 minutes
9. Second post-BD spirometry will be performed and post-BD FEV_1 measurement will be obtained. If the incremental change in the second post-BD spirometry assessment:
   - is ≤ 5% increase, then no more SABA will be given and the assessment is complete.
   - is > 5% increase, then 2 additional puffs of SABA will be administered as above in Steps 2 and 3, with a 30-second interval between puffs. Then a third post-BD spirometry assessment will be performed 15-20 minutes later.

The % difference comparing FEV_1 after 6 puffs to FEV_1 after 4 puffs will be calculated as follows:

$$\% \text{ difference} = FEV_1 \text{ (6 puffs)} - FEV_1 \text{ (4 puffs)}/FEV_1 \text{ (4 puffs)} \times 100$$

The highest pre- and post-BD FEV_1 obtained after 4, 6, or 8 puffs will be used to determine reversibility and for analysis.

Reversibility is calculated as follows:

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

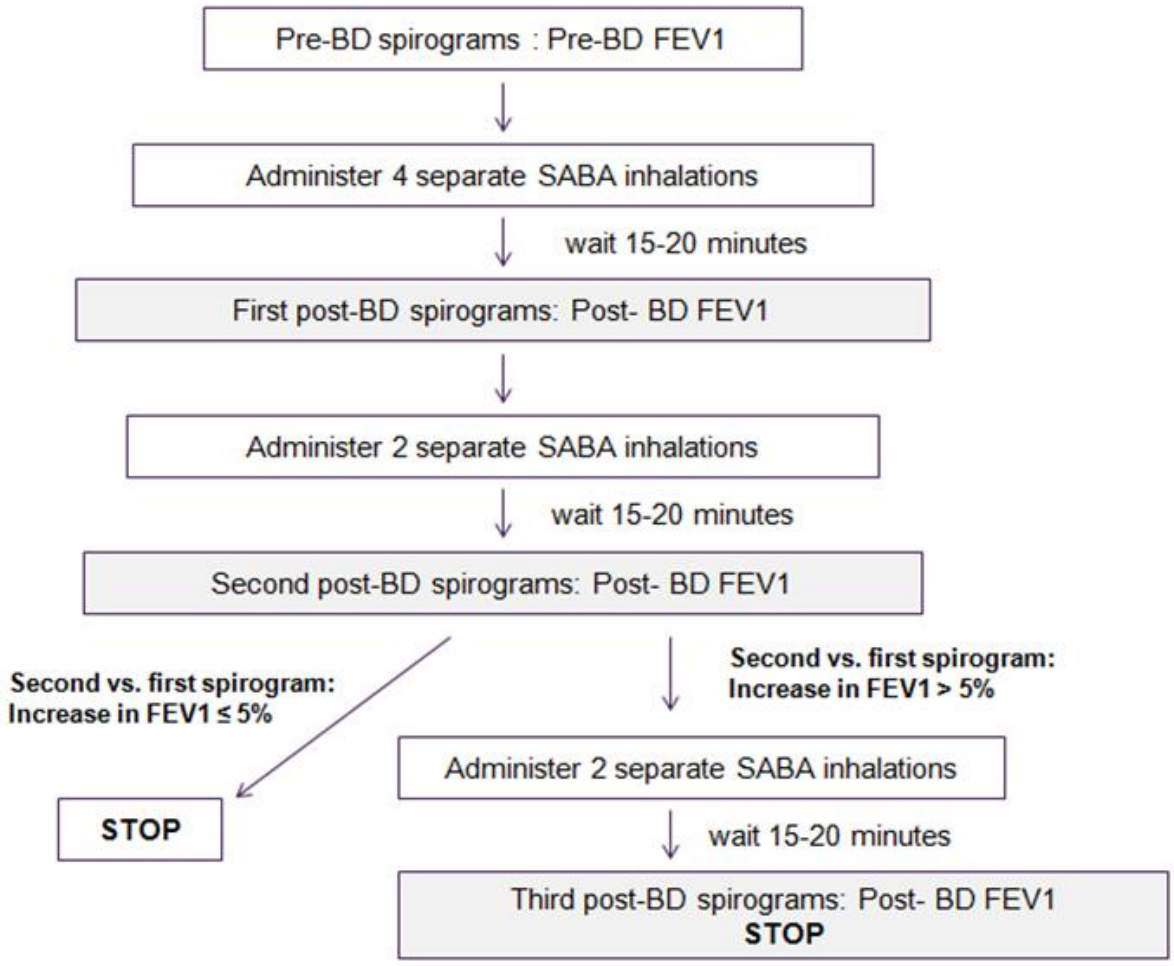

Figure 4.3.1.3-1 Reversibility Algorithm

FEV_1 = forced expiratory volume in 1 second; post-BD = post bronchodilator; pre-BD = pre-bronchodilator; SABA = short-acting β2 agonist

4.3.1.4 Home Peak Flow Testing

An electronic, hand-held spirometer (peak flow meter) will be dispensed to the subject on Visit 2 (Week -4) once the subject has met preliminary eligibility criteria (see Section 4.1.2 and Section 4.1.3).

Home peak flow testing for peak expiratory flow rate (PEFR) will be performed twice daily, in the morning upon awakening and in the evening prior to bedtime using a peak flow meter (see Section 4.3.2 for information on peak flow meter and ePRO device) from the morning of Visit 2 (Week -4) through Week 64. When possible, ambulatory lung function measurements should be taken at least 6 hours after the last dose of SABA rescue medication.

Subjects should perform 3 successive peak flow maneuvers while sitting or standing, but in the same position at every testing. The highest of the 3 values will be captured for each timepoint.

At each study visit, the investigator/authorized delegate will check the subject's compliance with the peak flow measurements and will check that the subject is using the peak flow meter correctly.

4.3.1.5 Healthcare Resource Utilization

Healthcare resource utilization will be collected by the investigator or designee at each study visit after randomization and will be recorded on the eCRF.

4.3.2 Patient Reported Outcomes

Subjects will receive an ePRO device and a hand-held spirometer at Visit 2 (Week -4) to be used for completion of PRO assessments (ie, Asthma Daily Diary, ACQ-6, AQLQ[S]+12, WPAI+CIQ, EQ-5D-5L) and home peak flow testing. The study center staff will be trained on how to use the devices and will be responsible for instructing subjects on how to use both devices. Subjects will have an opportunity to practice using the devices through a pre-programmed training module. Subjects should be informed that the recordings made electronically cannot be retrospectively or prospectively entered and must be completed within a defined time window. Subjects will also be provided with information about when and where to request help if problems occur.

Subjects must bring the ePRO device to each study visit, and compliance with all PRO assessments and home peak flow testing will be checked by center staff.

4.3.2.1 Asthma Daily Diary

The Asthma Daily Diary includes the following daily assessments: asthma symptoms; inhalations of rescue medication; nighttime awakening due to asthma requiring rescue medication use, asthma-related activity limitations, asthma-related stress, and background medication compliance.

The Asthma Daily Dairy will be completed each morning and evening. There will be triggers in the ePRO device to alert the subjects to signs of worsening of asthma and to contact the investigator (see Section 4.3.1).

4.3.2.2 Asthma Control Questionnaire-6

The ACQ is a patient-reported questionnaire assessing asthma symptoms (ie, night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing) and daily rescue bronchodilator use and FEV_1 (Juniper et al, Oct 1999). The ACQ-6 is a shortened version of the ACQ that omits the FEV_1 measurement from the original ACQ score. 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 0.75 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).

The study center staff will provide initial training on the ePRO device at Visit 1 (Week -5) in order for the subject to complete the screening ACQ-6 at the study center. The ePRO device will remain at the study center until Visit 2 (Week -4).

At Visit 2 (Week -4), study center staff will provide training as described in Section 4.3.2 and will give the subject the ePRO device to take home. The subject will complete the ACQ-6 weekly during the Screening/Run-in period. The Visit 2 (Week -4), Visit 3 (Week -1), and Visit 4 (Week 0, Day 1) ACQ-6 will be completed at the study site on the ePRO device. Subjects will be prompted to complete the ACQ-6 at Week -3 and Week -2 at home on the ePRO device. Once randomized, subjects will be prompted to complete the ACQ-6 every 2 weeks at home on the ePRO device through Week 64.

Subjects must have an ACQ-6 score of ≥ 1.5 twice during screening. The first time must be at Visit 1 (Week -5). If the ACQ-6 score is not ≥ 1.5 at Visit 1 (Week -5), then the subject should not continue in the study (screen failure). The second time the subject must have an ACQ-6 score of ≥ 1.5 may be at either Week -2 (at home on the electronic patient-reported outcome [ePRO] device) or at Visit 3 (Week -1).

4.3.2.3 Asthma Quality of Life Questionnaire, Standardised (AQLQ[S])+12

The AQLQ(S)+12 is a 32-item questionnaire that measures the HRQoL experienced by asthma patients (Juniper et al, May 1999). 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 a minimally important change, with score changes of ≥ 1.5 identified as large meaningful changes (Juniper et al, 1994).

The questionnaire will initially be completed at the study center on Visit 4 (Week 0, Day 1) on the ePRO device. Subjects will then be prompted to complete the AQLQ(S)+12 every 4 weeks at home on the ePRO device through Week 64.

4.3.2.4 Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ)

The WPAI+CIQ will be used to measure self-reported productivity loss and consists of questions about how asthma and asthma-related issues impact the subject's ability to work, attend class, and perform regular activities of daily living within the previous 7 days.

The questionnaire will initially be completed at the study center on Visit 4 (Week 0, Day 1) on the ePRO device. Subjects will then be prompted to complete the WPAI+CIQ every 2 weeks at home on the ePRO device through Week 52.

4.3.2.5 EQ-5D-5L European Quality of Life-5 Dimensions, 5 Level Version

The EQ-5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty.

The subject will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the subject will be asked to rate current health status on a scale of 0-100, with 0 being the worst imaginable health state.

The questionnaire will initially be completed at the study center on Visit 4 (Week 0, Day 1) on the ePRO device. Subjects will then be prompted to complete the EQ-5D-5L weekly at home on the ePRO device through Week 52.

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

4.3.3.1 Medical and Asthma History

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

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

4.3.3.2 Physical Examination Weight, Height

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

Height will be measured at Visit 1 (Week -5) only.

4.3.3.3 Vital Signs

Vital signs (blood pressure, temperature, pulse rate, and respiration rate) will be obtained before investigational product administration on all treatment days. After investigational product administration, subjects will be monitored for immediate drug reactions; vital signs will be taken 60 and 120 minutes (± 5 minutes) after the first 5 doses of investigational product are administered, and 60 minutes (± 5 minutes) after the sixth and subsequent doses of investigational product are administered. If the subject is not stable, vital signs should be monitored at least hourly until the subject is discharged from the study center.

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

4.3.3.4 Electrocardiogram

In a Phase 1 study with healthy subjects, no effects of MEDI9929 were observed in cardiac electrophysiological intervals. An ECG sub-study will be performed in this study to confirm that MEDI9929 does not affect QT/QTc intervals in the target population of patients with inadequately controlled, severe asthma. Approximately 160 subjects will take part in the sub-study. The size of this subset will allow for characterization of QT/QTc effects and further support the safety profile of MEDI9929 with respect to QT/QTc and other ECG data.

Computerized triplicate 12-lead ECG recordings will be obtained as part of the ECG sub-study from all subjects until the approximately 40 subjects in each treatment arm have completed the study, and will be transmitted to a central reader to quantitatively assess PR, QRS, QT, and QTc intervals.

Once there are sufficient data for the sub-study, the sponsor or designee will communicate this to all participating study sites, and from that timepoint on, only one 12-lead ECG recording will be obtained, and the ECGs tracings will not be transmitted to a central reader.

The ECG assessments will be performed in accordance with the schedule of study procedures, at the same time of day and prior to blood drawing, FE_{NO}, spirometry, and administration of investigational product. The same ECG machine is to be used for the assessment throughout the subject's participation in the study.

The subjects should be instructed to refrain from taking their usual asthma controller medication (see Table 4.3.3.4-1) prior to scheduled ECG assessment. The medication restriction is waived for the screening ECG at Visit 1 (Week -5).

Table 4.3.3.4-1 Prohibited Medications and Minimum Time Intervals Prior to Electrocardiogram Testing

Concomitant Medication	Minimum Time Interval from Last Medication Dose to ECG Testing
Short-acting bronchodilators (eg, SABA [albuterol/salbutamol]), short acting anti-cholinergics (eg, ipratropium)	6 hours
Long-acting bronchodilators (eg, LABA, LAMA)	12 hours

ECG = electrocardiogram; LABA = long-acting β2 agonist; LAMA = long-acting anti-muscarinics; SABA = short-acting β2 agonist

The ECGs will begin after the subject has been supine for at least 10 minutes. Each tracing will be separated by approximately 1 minute. Each lead will be recorded for at least 3-5 beats at a speed of 25 mm/second paper speed and 10 mm/mV amplitude. Heart rate, PR, QRS, QT and QTc intervals (millisecond) will be recorded from the 12-lead ECG.

The principal investigator or a designated subinvestigator will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. Printouts of the ECG will be signed, dated, and stored at the study center with the subject's source documents. In addition, ECG data and evaluations (eg, clinical significance) will be recorded in the eCRF. Further details on recording computerized ECG recordings will be provided in a separate manual.

4.3.4 Clinical Laboratory Tests

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

Clinical laboratory safety tests including serum pregnancy tests will be performed in a central clinical laboratory. In addition to the safety laboratory hematology samples at the central clinical laboratory, a complete blood count with differentials will be performed at the site's local laboratory at Visit 1 (Week -5) and Visit 3 (Week -1). The Visit 3 (Week -1) blood eosinophil count from the local laboratory will be used for stratification.

Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed (see Table 4.2.1-1, Table 4.2.2-1, Table 4.2.2-2, Table 4.2.3-1 for the schedule of tests):

Serum Chemistry

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

Note for serum chemistries: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently. In the event that the AST or ALT is elevated ≥ 3 × ULN, creatine kinase will be measured.

Hematology

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hematocrit
- Hemoglobin
- Platelet count

Urinalysis

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

Pregnancy Test

Serum beta-hCG (at screening only, required of all females)
Urine human chorionic gonadotropin (hCG, required for females of childbearing potential only)

Other Safety Tests

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

4.3.4.1 Tuberculosis Testing

All subjects will have the QFT-G test, which will be performed by the central clinical laboratory.

If a subject has an indeterminate QFT-G test at screening, the chest x-ray shows no evidence of active TB, there are no signs or symptoms of active TB, there is no recent contact with

anyone with active TB, and there is no history of latent (unless diagnosed within the 3 years prior to screening with documentation of completion of appropriate treatment) or active TB, the subject may be randomized and will have additional QFT-G testing performed at Weeks 12, 28, 40, and 52. Additionally, if in the opinion of the principal investigator and after discussion with the medical monitor, an expert specializing in TB may be consulted prior to randomization. If, during the study, a subject is determined to have a positive QFT-G result, the local country guidelines should be consulted for acceptable anti-TB treatment regimens. If no local guidelines exist for immunocompromised individuals, then USA guidelines must be followed.

4.3.5 Pharmacokinetic Evaluation and Methods

Blood samples for MEDI9929 concentration determination will be collected prior to administration of investigational product according to the schedule of study procedures. MEDI9929 concentrations in serum will be measured by enzyme-linked immunosorbent assay. Instructions for sample collection, processing, storage, and shipment can be found in a laboratory manual provided to the sites.

4.3.6 Immunogenicity Evaluation and Methods

Serum samples to measure the presence of ADA will be collected prior to administration of investigational product according to the schedule of study procedures. If the subject discontinues the study early and does not agree to return for the 12 weeks of follow-up, an ADA sample will be collected at the EDV (see Section 4.1.6). Confirmed ADA-positive samples will be tested using a neutralizing antibody assay.

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

4.3.7 Biomarker Evaluation and Methods

Serum Biomarkers

Serum will be collected during the study to evaluate changes in biomarkers related to asthma, Th2 inflammation, and the TSLP pathway. Baseline levels of serum biomarkers will also be used to identify predictive biomarkers of MEDI9929 response, including IgE fluorescence enzyme immunoassay for common aeroallergens to identify those with atopic asthma. The specific biomarkers that will be analyzed are cytokines, chemokines and inflammatory mediators associated with asthma and the TSLP pathway.

Flow Cytometry

Whole blood samples will be collected during the study at selected sites to evaluate intracellular cytokines in T cells by flow cytometry following *ex vivo* stimulation by phorbol myristate acetate.

Deoxyribonucleic Acid

Whole blood will be collected at a single timepoint Visit 4 (Week 0, Day 1) after subjects have been randomized into the study for extraction of DNA and analysis of polymorphisms associated with asthma, TSLP or MEDI9929 response. The collection of blood for DNA analysis is optional and subjects who do not wish to have the DNA test done will still be eligible for the study. The completion of a separate informed consent form (ICF) related to DNA is required. Subjects who elect to have the DNA test done may, at any time before the end of the study, request that the blood collected for DNA analysis be destroyed.

4.3.8 Estimate of Volume of Blood to Be Collected

The estimated volume of blood to be collected from each subject at each visit (and across all visits) from screening through the Week 64 is presented in Table 4.3.8-1.

Table 4.3.8-1 Estimated Blood Volume to be Collected by Visit

Visit Week	Visit Number	Estimated Blood Volume (mL)
-5	1	15.0
-3	2	0.0
-1	3	10.0
0	4	40.0 [a, b]
2	5	0.0
4	6	25.0
6	7	0.0
8	8	0.0
10	9	0.0
12	10	30.0 [b, c]
14	11	0.0
16	12	0.0
18	13	0.0
20	14	25.0
22	15	0.0
24	16	0.0
26	17	0.0

Table 4.3.8-1 Estimated Blood Volume to be Collected by Visit

Visit Week	Visit Number	Estimated Blood Volume (mL)
28	18	30.0 [b, c]
30	19	0.0
32	20	0.0
34	21	0.0
36	22	0.0
38	23	0.0
40	24	26.0 [c]
42	25	0.0
44	26	0.0
46	27	0.0
48	28	0.0
50	29	0.0
52	30	30.0 [b, c]
58	31	0.0
64	32	28.0 [b]
Total		**259.0**

DNA = deoxyribonucleic acid; QFT-G = QuantiFERON® -tuberculosis Gold

[a] This includes 8.5 mL of blood for the optional DNA analysis

[b] This includes 4 mL of blood for the flow cytometry, which is only being collected at selected study sites

[c] Includes 3-mL sample for QFT-G, which will only be collected from subjects found to have indeterminate QFT-G at screening

4.4 Study Suspension or Termination

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

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

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

MedImmune will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the Institutional Review Board/Independent Ethics Committee (IRB/IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Products

MedImmune will provide the investigators with investigational products (Table 4.5.1-1) using designated distribution centers.

Table 4.5.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
MEDI9929 (AMG 157)	Amgen	70 mg/mL MEDI9929 formulated with 10 mM sodium acetate, 9% (w/v) sucrose, and 0.004% (w/v) polysorbate 20, pH 5.2
Placebo	Amgen	Placebo contains the same excipients, in the same concentration only lacking MEDI9929

(w/v) = weight by volume

Excipients include sodium acetate, sucrose, and polysorbate 20.

Investigational product will be supplied to the site in open-label kits with10 vials of either MEDI9929 or placebo. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton).

4.5.1.1 Investigational Product Dose Preparation

Investigational Product Inspection

Each vial should be visually inspected by the unblinded investigational product manager prior to dose preparation. The investigational product will be provided to the study sites as a colorless to slightly yellow clear 1 mL solution (70 mg/mL) contained in 5 mL single use glass vials to be stored frozen at -20°C to -70°C until used.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.4) for further instructions.

Dose Preparation Steps

MEDI9929 does not contain preservatives and any unused portion must be discarded. Preparation of MEDI9929 is to be performed aseptically. Total in-use storage time from needle puncture of the investigational product vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C. If storage time exceeds these limits, a new dose must be prepared from new vials/syringes.

To prepare the subject's dose, the unblinded investigational product manager will select investigational product for administration according to the kit identification numbers assigned by the IXRS.

Allow the vials to thaw in the dark, at room temperature (20°C to 25°C) for up to 2 hours. Vials should be checked for cracks or damage that may occur if the thawing process is not performed properly. Damaged product should not be administered and the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.4) for further instructions.

Do not disturb the vials during the thaw, except to gently swirl to check for completion of thaw. Do not refreeze the vials once set up for thaw. Never shake vials vigorously, especially during the thawing process.

Five vials of investigational product will be assigned by IXRS for each dose. To prepare the investigational product for administration, the unblinded investigational product manager should remove the tab portion of the vial cap and clear the stopper with 70% ethyl alcohol or equivalent. Assigned vials should be used at one time to prepare the dose required at each

visit. Unused product in opened and dispensed vials should not be used for subsequent dosing and should be stored for investigational product accountability.

Doses of investigational product will be administered by 3 injections (see Table 3.1.2-1) and must be prepared using plastic disposable syringes and aseptic technique by the unblinded investigational product manager/unblinded study personnel as presented in Table 4.5.1.1-1. Each syringe will be numbered by the unblinded investigational product manager in the order they are prepared. The 1-mL syringe will always be No. 1.

Table 4.5.1.1-1 Dose Preparation

Treatment Arm	Dose	Dose Preparation Instruction	Syringe
1	Placebo 5 vials placebo	**Step 1**: Withdraw 1 mL of placebo using a 1-mL syringe with a 19-gauge needle Remove the 19-gauge needle Replace with a 27-gauge 1/2-inch needle and cap until administration **Label syringe as No. 1**	1 mL
		Step 2: Withdraw 0.5 mL of placebo using a 3-mL syringe with a 19-gauge needle Remove the 19-gauge needle Replace with another 19-gauge needle and cap Set vial aside	3 mL
		Step 3: With the same syringe used in Step 2, withdraw 1 mL of placebo for a total volume of 1.5 mL Remove the 19-gauge needle Replace with a 27-gauge 1/2-inch needle and cap syringe until administration **Label syringe as No. 2**	
		Step 4: Repeat Steps 2 and 3 for remaining 2 placebo vials **Label syringe as No. 3**	3 mL
2	70 mg 1 vial MEDI9929 4 vials placebo	**Step 1:** Withdraw 1 mL of MEDI9929 using a 1-mL syringe with a 19-gauge needle Remove the 19-gauge needle Replace with a 27-gauge 1/2-inch needle and cap until administration **Label syringe as No. 1**	1 mL
		Step 2: Withdraw 0.5 mL of placebo using a 3-mL syringe with a 19-gauge needle Remove the 19-gauge needle Replace with another 19-gauge needle and cap Set vial aside	3 mL
		Step 3: With the same syringe used in Step 2, withdraw 1 mL of placebo for a total volume of 1.5 mL Remove the 19-gauge needle Replace with a 27-gauge 1/2-inch needle and cap syringe until administration **Label syringe as No. 2**	

Table 4.5.1.1-1 Dose Preparation

Treatment Arm	Dose	Dose Preparation Instruction	Syringe
		Step 4: Repeat Steps 2 and 3 for remaining 2 placebo vials **Label syringe as No. 3**	3 mL
3	210 mg 3 vials MEDI9929 2 vials placebo	**Step 1**: Withdraw 1 mL of MEDI9929 using a 1-mL syringe with a 19-gauge needle Remove the 19-gauge needle Replace with a 27-gauge 1/2-inch needle and cap syringe until administration **Label syringe as No. 1**	1 mL
		Step 2: Withdraw 0.5 mL of placebo using a 3-mL syringe with a 19-gauge needle Remove the 19-gauge needle Replace with another 19-gauge needle and cap Set vial aside	3 mL
		Step 3: With the same syringe used in Step 2, withdraw 1 mL of MEDI9929 for a total volume of 1.5 mL Remove the 19-gauge needle Replace with a 27-gauge 1/2-inch needle and cap syringe until administration **Label syringe as No. 2**	
		Step 4: Repeat Steps 2 and 3 for remaining one placebo vial and one MEDI9929 vial **Label syringe as No. 3**	3 mL
4	280 mg 5 MEDI9929 vials	**Step 1**: Withdraw 1 mL of MEDI9929 using a 1-mL syringe with a 19-gauge needle Remove the 19-gauge needle Replace with a 27-gauge 1/2-inch needle and cap syringe until administration **Label syringe as No. 1**	1 mL
		Step 2: Withdraw 0.5 mL of MEDI9929 using a 3-mL syringe with a 19-gaugeG needle Remove the 19-gauge needle Replace with another 19-gauge needle and cap Set vial aside	3 mL
		Step 3: With the same syringe used in Step 2, withdraw 1 mL of MEDI9929 for a total volume of 1.5 mL Remove the 19-gauge needle Replace with a 27-gauge 1/2-inch needle and cap syringe until administration **Label syringe as No. 2**	
		Step 4: Repeat Steps 2 and 3 for remaining 2 MEDI9929 vials **Label syringe as No. 3**	3 mL

Note: Used vials should not be discarded. These will be kept for investigational product accountability.

4.5.1.2 Treatment Administration

The first day of dosing is considered Day 1. The investigational product will be administered with 3 (2 × 1.5 mL and 1 × 1 mL) SC injections Q2W.

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

The 3 required injections should be administered using separate injection sites on the anterior thigh, abdomen, or upper arm. Injections administered in the same location should be at least 1-inch apart. The upper arm should only be used for the smaller volume (1 mL) injections. Subjects who have a history of mastectomy with lymph node dissection should not have any study medication administered in the affected arm.

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

- The subject received allergen immunotherapy injection on the same day as scheduled investigational product administration
- The subject has an intercurrent illness that in the opinion of the investigator and/or medical monitor may compromise the safety of the subject in the study (eg, viral illnesses)
- The subject, in the opinion of the investigator, is experiencing an acute or emerging asthma exacerbation
- The subject is febrile (≥ 38°C; ≥ 100.4°F) within 72 hours prior to investigational product administration

If the subject reports an injection site reaction, the investigator or qualified designee will complete the AE eCRF page and an additional eCRF page with questions about the injection site reaction.

Rotation of Injection Sites

It is advised that the site of injection be rotated and the subject gets investigational product injections in different anatomical sites at each treatment visit. Suggested scheme of the

injection site rotation is shown in Figure 4.5.1.2-1. For ease or tracking injection sites, suggested investigational product administration locations for one study visit may be: one injection in right upper arm, one injection in right abdomen, and one injection in right anterior thigh. Each syringe number and corresponding injection site must be documented on the eCRF and in the source documents (eg, syringe No. 1 upper arm [Site 1 or 4], syringe No. 2 abdomen [Site 2 or 5], syringe No. 3 anterior thigh [Site 3 or 6]) at each treatment visit.

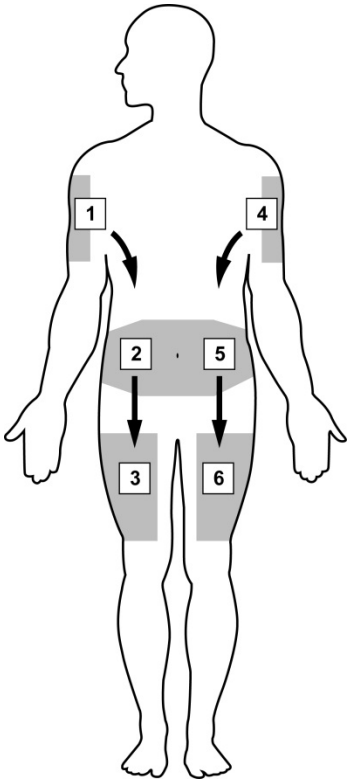

Figure 4.5.1.2-1 Rotation of Injection Sites

In cases when rotation of the injection site is not feasible and/or the subject prefers not to rotate injection sites, the reason for not rotating the injection site should be documented in the source documents.

4.5.1.3 Monitoring of Dose Administration

For the first 2 doses of investigational product, subjects will remain at site for a minimum of 2 hours or until stable, whichever is later. For the third and subsequent doses of investigational product, subjects will remain at site a minimum of 1 hour or until stable, whichever is later. Discharge from site will be determined by the investigator.

Vital signs (blood pressure, temperature, pulse rate, and respiration rate) will be obtained before investigational product administration on all treatment visits. After investigational

product administration, subjects will be monitored for immediate drug reactions; vital signs will be taken 60 and 120 minutes (± 5 minutes) after the first 2 doses of investigational product are administered, and 60 minutes (± 5 minutes) after the third and subsequent doses of investigational product are administered. If the subject is not stable, vital signs should be monitored at least hourly until the subject is discharged from the study center.

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

4.5.1.4 Reporting Product Complaints

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

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com
Phone: 1-301-398-2105
1-877-MEDI-411 (1-877-633-4411)
Fax: 1-301-398-8800

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

4.5.2 Additional Study Medications

All subjects will be taking medium- or high-dose ICS and LABA (see Appendix 5 for equivalent ICS doses) from Week -4 through Week 64. The cost of the ICS and LABA treatment will be reimbursed to the sites by the sponsor, where applicable.

If at Week -4 the subject is also taking additional asthma controller medications (including leukotriene modifiers, theophylline, cromones, or OCS up to a maximum of 10 mg daily or 20 mg every other day), then these medications should be continued at a stable dose during the screening/run-in period and to Week 64. Subjects who are taking theophylline should be monitored appropriately by the investigator during the conduct of this study.

The principal aim of this study is to establish the treatment effect of MEDI9929 as an 'add on' therapy; therefore, it is highly desirable that background asthma controller medications are maintained at a stable dose from Week -4 through Week 64, in order to prevent any independent confounding of that treatment effect. Symbicort® should not be used as a rescue inhaler (eg, SMART regimen). However, if the investigator considers a permanent change to background medications between Week-4 (Visit 2) and Week 64 to be necessary, the change should be discussed with the sponsor's medical monitor and must be noted in the eCRF. The subject may remain in the study unless the addition of omalizumab is required, in which case the subject must be withdrawn.

During the study, subjects may use an inhaled short-acting bronchodilator or an inhaled short-acting anticholinergic on an as-required basis as a reliever or rescue medication.

4.5.3 Labeling

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

4.5.4 Storage

Store investigational product frozen at -20°C to -70°C until thawing for dose preparation.

4.5.5 Treatment Compliance

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

4.5.6 Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to

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

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

An IXRS 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 or designee notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of blinded investigational product kit numbers to the subject.

Prior to randomization, subjects will be stratified by study site (non-Japanese and Japanese), then subjects will be stratified by blood eosinophil count (≥ or < 250 cells/μL) and by ICS dose level (medium or high). Subjects taking maintenance OCS will be automatically assigned to the high-dose ICS strata. There will be a total of 8 strata; 4 strata for non-Japanese subjects and 4 identical strata for Japanese subjects (see Section 3.1.1 for strata descriptions).

Subjects will then be randomized at a 1:1:1:1 ratio to receive either MEDI9929 (280 mg [Q2W], 210 mg [Q4W], or 70 mg [Q4W]) or placebo.

Investigational product (MEDI9929 or placebo) must be administered the same day the investigational product is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified *immediately*.

4.6.2 Methods for Ensuring Blinding

This is a double-blind study in which MEDI9929 and placebo are not identical in appearance. Neither the subject/legal representative nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Conference on Harmonisation [ICH] E9) (see Section 4.6.2.3 for unblinding related to interim analysis). Since MEDI9929 and the placebo are not identical, an unblinded investigational product manager will prepare the investigational product. Once the investigational product is in the dosing syringes, MEDI9929 and placebo are indistinguishable, so the investigational product will be administered by a blinded study team member. An unblinded investigational product monitor will perform investigational product accountability. In the event that treatment allocation for a subject becomes known to the

investigator or other study staff involved in the management of study subjects, the sponsor must be notified *immediately*. The site will maintain a written plan detailing which staff members are blinded/unblinded and the process of investigational product administration used to maintain the blind.

4.6.2.1 Unblinding Due to Possible Effect of MEDI9929

MEDI9929 may reduce eosinophil counts in the blood over time. As a precaution, eosinophil, basophil, and monocyte results on central laboratory reports will not be communicated to the site personnel once subjects receive investigational product.

4.6.2.2 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IXRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded. If a subject is unblinded, the investigator should contact the study monitor and/or medical monitor ***immediately***. If a subject is unblinded by the investigator, the subject will not receive any more investigational product.

MedImmune retains the right to unblind the treatment allocation for subjects who have SAEs that are unexpected, suspected to be causally related to the investigational product, and that potentially require expedited reporting to regulatory authorities. If a subject's investigational product allocation is unblinded, the subject will be discontinued from investigational product. Only limited Patient Safety and Regulatory Affairs personnel, not associated with the conduct of the study, will be unblinded to the subject's treatment allocation. There may be instances where, in the opinion of the investigator and medical monitor, the risk-benefit assessment is favorable for the subject to remain in the study and continue receiving investigational product. These instances will be handled on a case-by-case basis. The decision to continue treatment will be fully documented in the trial master file.

4.6.2.3 Unblinding for Interim Analysis Purposes

An interim analysis will be conducted for this study as described in Section 4.8.7. To ensure the blinding of each subject's treatment assignment throughout the study, both the Stage I analysis and the interim analysis, will be performed by a limited number of sponsor

personnel who are not directly involved in the conduct of the study. Study site personnel and sponsor personnel directly associated with the conduct of this study and the subjects will remain blinded to the treatment assignment for individual subjects until the completion of the study. Details of the interim analysis will be specified in the interim analysis plan prior to unblinding.

4.6.2.4 Unblinding for Safety Analysis by Data and Safety Monitoring Board

Blinded and unblinded information will be provided to the independent Data and Safety Monitoring Board (DSMB) according to the DSMB charter and the study unblinding plan (see Section 4.8.8 for the DSMB overview). The DSMB will be provided data that are summarized by treatment group using masked treatment group labels (eg, A, B, C, and D) to review safety data throughout the study and make recommendations regarding further study conduct as required. After reviewing the data by treatment group, the DSMB may unblind a treatment group for additional review. The sponsor will remain blinded to all data transfers provided to the DSMB (see Section 4.6.2.2 for information about unblinding for SAEs).

4.7 Restrictions During the Study and Concomitant Treatment(s)

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

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “excluded” as listed in Section 4.7.2. Specifically, subjects should receive full supportive care during the study, including treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

In addition to the background asthma medications and rescue medications described in Section 4.5.2, the following concomitant medications related to asthma/allergy treatment are permitted from screening (Week -5) through Week 64:

- Mucolytics and expectorants not containing bronchodilators.
- Maintenance regimen of allergen-specific immunotherapy is allowed but should not be administered on the same day as investigational product. Subjects should have

commenced the regimen for at least 2 months prior to Visit 1 and should remain on a maintenance regimen throughout the study.

- Topical, nasal, and/or ocular formulations of corticosteroids or cromones.
- Topical or oral antihistamines.
- Inactivated vaccines.

4.7.2 Prohibited Concomitant Medications

Other than the medications described above, use of concomitant medications including over-the-counter medications, herbal supplements, vitamins, etc, from screening (Week -5) through Week 64 is discouraged. Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

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

- Immunosuppressive medication (eg, methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid).
- Oral corticosteroids for chronic use in diseases other than asthma; short bursts (≤ 7 days) of systemic corticosteroids for other acute inflammatory diseases are. permitted
- 5-lipoxygenase inhibitors (zileuton).
- Investigational agents other than MEDI9929.
- Marketed biologics including omalizumab.
- Immunoglobulin or blood products.
- Use of any oral or ophthalmic β-adrenergic antagonist (eg, propranolol).
- Live or attenuated vaccines.
- Subjects are not to begin allergen-specific immunotherapy from 2 months before Visit 1 (Week -5) through Week 64.
- Th2 cytokine inhibitor (suplatast).

See also Table 4.3.1.3-1 for prohibited medications prior to spirometry assessment.

4.8 Statistical Evaluation

4.8.1 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 two-sided and all efficacy analyses will be conducted with a two-sided test at the 0.1 significance level, unless otherwise stated. Baseline value will be defined as the last valid assessment prior to the first administration of investigational product on Day 1.

No missing data will be imputed for the primary endpoint. Missing data imputation methods for the secondary endpoints will be specified in the statistical analysis plan (SAP). The primary endpoint will be tested using a stepdown method for 3 hypotheses (from the high dose [280 mg Q2W] to the medium dose [210 mg Q4W] to the low dose [70 mg Q4W] when compared with placebo) to maintain the overall type-1 error rate at 0.1 (two sided). Nominal p-values will be provided for the selected secondary efficacy endpoints (pulmonary function, ACQ-6, AQLQ(S)+12, and Asthma Daily Diary) without multiplicity adjustment.

For the selected secondary efficacy endpoints that are continuous variables, a generalized linear mixed model using a linear contrast test including treatment group, visit, treatment-by-visit interaction, baseline blood eosinophil count ($\geq$ or $<$ 250 cells/μL), baseline ICS dose level (medium or high), and the respective baseline measure for the given endpoint as fixed effects may be used to compare the change from baseline at Week 52 for each efficacy endpoint between the individual MEDI9929 dose groups and the placebo group, respectively. No p-values will be reported for other PROs. Additional details of statistical analyses will be described in the SAP.

The intent-to-treat (ITT) population is defined as all subjects who are randomized and receive any investigational product. Treatment group will be assigned according to the initial randomization, regardless of whether subjects receive an investigational product different from that to which they were randomized. This is the primary efficacy population.

The per protocol (PP) population is defined as all subjects that do not have significant protocol violations, and have received at least 80% of the intended doses of investigational product. Exclusions from the PP population will be made prior to Stage 1 analysis (see Section 4.8.7).

The as-treated population is defined as all subjects that receive any investigational product. The safety analyses will be presented on an as-treated basis. Additional details of assigning subjects to a treatment group will be described in the SAP.

The evaluable population for PK is defined as all subjects that receive any investigational product and have a sufficient number of serum concentration measurements for computing PK parameters.

Details of each population above and any additional population, if needed, will be described in the SAP.

4.8.2 Sample Size and Power Calculations

Sample size calculations have been performed for the primary endpoint of annualized AER, based on the negative binomial distribution (Keene et al, 2007). Approximately 552 subjects will be randomized in the study, with approximately 85% of the total number of subjects designated as non-Japanese subjects (ie, subjects enrolled at sites outside of Japan) and approximately 15% of the total number of subjects designated as Japanese subjects (ie, subjects enrolled at sites in Japan). The total enrollment may exceed 552 subjects depending on whether additional non-Japanese subjects are enrolled to mitigate for slow enrollment in Japan, and to accommodate subjects in screening/run-in when the different strata are closed to enrollment.

Subjects will be randomized in a 1:1:1:1 ratio to receive one of 3 dose levels of SC MEDI9929 (280 mg Q2W, 210 mg Q4W, or 70 mg Q4W) or placebo Q2W for 52 weeks. Prior to randomization, subjects will be stratified by study site (non-Japanese and Japanese) and then by blood eosinophil count (≥ or< 250 cells/μL) and ICS dose level (medium or high). Subjects taking maintenance OCS will be automatically assigned to the high-dose ICS strata. At least 50% of the total subjects will be enrolled in the high blood eosinophil stratum (≥ 250 cells/μL), and at least 40% of the subjects in each blood eosinophil stratum will be receiving high-dose ICS. Details on the 8 strata (4 strata for non-Japanese subjects and 4 identical strata for Japanese subjects) are included in Section 3.1.1.

The primary analysis will be based on the ITT population. The 3 primary comparisons are as follows: MEDI9929 280 mg Q2W versus placebo; MEDI9929 210 mg Q4W versus placebo; and MEDI9929 70 mg Q4W versus placebo. A total of 124 subjects per treatment group would be required to detect a 40% reduction in the annual AER for each MEDI9929 dose group compared to placebo group, assuming an AER of 0.7 in the placebo group, a two-sided significance level of 0.1, 80% power, and a dispersion parameter of 0.7 based on the negative binomial distribution. The AER of 0.7 in the placebo group was estimated based on internal and external studies with a similar subject population (before considering dropouts). The dispersion parameter of 0.7 was selected from the mepolizumab study in subjects with severe, eosinophilic asthma (Pavord et al, 2012). Sample size was increased to 138 per

treatment group to accommodate a 10% loss of information due to dropouts. The minimal detectable difference is approximately 28% reduction in annual AER. Figure 4.8.2-1 provides power calculations based on varying sample sizes for a selected treatment effect of AER reduction of 40% and 50%. The minimum acceptable reduction in the annual AER of 40% for the study population was based upon an expected reduction of approximately 50% in a Th2-driven asthma population which appears to be achievable in competitors which target Th2 cytokines (eg, IL-13, IL-5) and a more modest reduction in a non-Th2 asthma population for which there are little data and no current competitors.

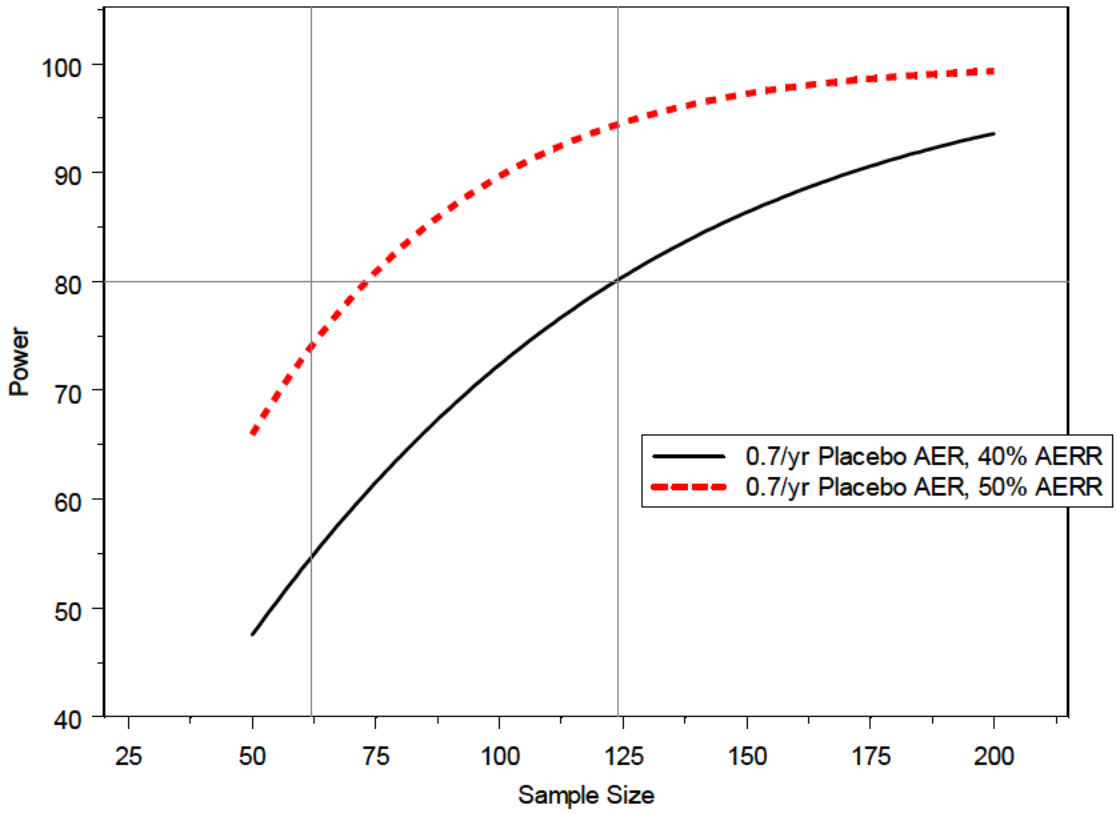

Figure 4.8.2-1 Power Calculations for an Annual Asthma Exacerbation Rate of 40 Percent or 50 Percent

AER = asthma exacerbation rate; AERR =asthma exacerbation rate reduction; yr = year
Note: The sample sizes do not reflect the projected dropout rate.

It is generally recommended that Japanese subjects be included in studies to identify inter-ethnic differences in the dose-response relationship early in clinical development. The target percentage of Japanese subjects for inclusion in this study is approximately 15% of the targeted enrollment of 552 subjects. A subgroup analysis of the non-Japanese subjects and Japanese subjects will be performed. Due to a small sample size, the subgroup analysis of the

Japanese subjects will not have sufficient power to detect differences with statistical significance.

4.8.3 Efficacy

4.8.3.1 Primary Efficacy Analysis

The primary objective of this study is to evaluate the effect of 3 dose levels of MEDI9929 on asthma exacerbations in adult subjects with inadequately controlled, severe asthma. The primary endpoint is a reduction in the annualized asthma exacerbation rate (defined in Section 4.3.1) measured at Week 52.

The annual AER will be presented as a weighted mean (total number of exacerbations for the treatment group divided by the total duration of person follow-up) per the joint guidelines recommended by the ATS/ERS. The primary endpoint analysis will be conducted using a negative binomial regression model with treatment group, baseline blood eosinophil count ($\geq$ or $<$ 250 cells/μL), and baseline ICS dose level (medium or high) as covariates. Because the treatment effect in the non-Japanese population is not expected to be different from the Japanese population, the stratification factor of study sites (non-Japanese or Japanese) will not be included as a covariate for the primary analysis. The follow-up time will be adjusted by offset option. The primary comparisons are as follows: MEDI9929 280 mg Q2W versus placebo; MEDI9929 210 mg Q4W versus placebo; and MEDI9929 70 mg Q4W versus placebo.

As a sensitivity analysis, the annual AER may be assessed by a Poisson regression model to assess the robustness with regard to the distributional assumptions. In a Poisson regression model, the correction for potential over-dispersion will be made by Pearson chi-square method. The same covariates used for the negative binomial regression model will be considered.

The primary analysis will be conducted based on the ITT population. As sensitivity and supportive analyses, the primary analysis may be repeated based on the PP population.

4.8.3.2 Secondary Efficacy Analyses

Efficacy Outcomes in Pre-specified Subpopulations of Asthma

The primary endpoint of a reduction in the annualized AER measured at Week 52 and two other secondary endpoints of change from baseline in FEV_1 and in overall symptom score at Week 52 will be analyzed by the following pre-specified subpopulations of asthma:

1) eosinophilic and non-eosinophilic; 2) Th2 high/low (Corren et al, 2011); 3) FE_{NO} high/low; 4) periostin high/low; 5) current post-BD FEV_1 reversibility; and 6) allergic and non-allergic asthma.

Pulmonary Function

The effect of MEDI9929 on pulmonary function as measured by pre- and post-BD FEV_1 and FVC at the site, and PEFR at home will be assessed during the study. Change from baseline in the mean values and percent change from baseline at various time points will be summarized using descriptive statistics. Change from baseline in the mean values and percent change from baseline of FEV_1 and FVC at Week 52 will be analyzed.

Additional Analyses of Asthma Exacerbation

The analysis of exacerbations will also be conducted specifically for severe asthma exacerbations (hospitalizations). In addition, asthma exacerbations and severe asthma exacerbations through Week 64 will also be summarized.

Time to first asthma exacerbation and time to first severe asthma exacerbation will be analyzed as a supportive efficacy analysis for the primary objective using a log-rank test. Incidence of asthma exacerbations will also be evaluated by the proportion of subjects having one or more asthma exacerbations and one or more severe asthma exacerbations during the study.

Optimal Dose and Regimen

Dose response may be evaluated based on quadratic and linear negative binomial regression models to detect the dose response. The E_{max} model may be generated to determine the minimum effective dose. The details of the dose response analysis will be described in the SAP.

4.8.3.3 Exploratory Analyses

Other Efficacy Outcomes in Pre-specified Subpopulations of Asthma

Three secondary endpoints of change from baseline in the mean ACQ-6 score, the overall AQLQ(S)+12 score, and total rescue medication use at Week 52 will be analyzed by following pre-specified subpopulations of asthma: 1) eosinophilic and non-eosinophilic;

2) Th2 high/low (Corren et al, 2011); 3) FE_{NO} high/low; 4) periostin high/low; 5) current post-BD FEV_1 reversibility; and 6) allergic and non-allergic.

Effect on Efficacy Outcomes Through the Safety Follow-up Period

Reduction in AER will be evaluated at Week 64. Change from baseline in lung function as measured by pre- and post-BD FEV_1 and FVC, in asthma symptoms (daytime and nighttime symptom frequency and severity, activity avoidance and limitation, asthma-related stress and fatigue as well as rescue medication use) as measured by the Asthma Daily Diary, asthma control as measured by the ACQ-6, and HRQoL as measured by the AQLQ(S) +12 will be evaluated.

Healthcare Resource Utilization

Healthcare resource utilization will be evaluated by the number and proportion of subjects who use a healthcare resource by Week 64.

WPAI+CIQ

The WPAI+CIQ provides employment and academic status as well as 4 types of scores: absenteeism (work/class time missed), presenteeism (impairment at work/in class or reduced on-the-job/classroom effectiveness), productivity loss (overall work/classroom impairment/absenteeism plus presenteeism), and activity impairment for regular activities. Absenteeism, presenteeism, productivity loss, and activity impairment for each treatment group will be evaluated and will be presented as the proportion of impairment.

Biomarkers

The relationship between changes in biomarkers and asthma, Th2 inflammation, and the TSLP pathway may be explored. Baseline serum blood biomarkers and FE_{NO} results will be explored to identify predictive biomarkers of MEDI9929 response. Three secondary endpoints of change from baseline in the mean ACQ-6 score, the overall AQLQ(S)+12 score, and total rescue medication use at Week 52 may be analyzed by TSLP-related biomarkers.

Biomarkers include cytokines, chemokines and inflammatory mediators associated with asthma and the TSLP pathway. Intracellular cytokines in T cells by flow cytometry following *ex vivo* stimulation by phorbol myristate acetate may also be evaluated.

DNA will be extracted and polymorphisms associated with asthma, TSLP or MEDI9929 response may be analyzed (optional for subjects).

These data will be reported separately from the clinical study report.

4.8.3.4 Subgroup Analyses

The subgroup analyses listed below, based on populations of interest, will be conducted at Week 52 on reduction in AER, change from baseline in FEV_1, and change from baseline in overall symptom score. The baseline variables listed below may also be assessed as covariates in a sensitivity analysis of the primary statistical model, if not already included, to assess any possible influence on the endpoints.

1. Peripheral blood eosinophil count ≥ 250 versus < 250 cells/μL
2. Th2 status: high: IgE > 100 IU/mL and blood eosinophil count ≥ 140 cells/μL versus low: IgE ≤ 100 IU/mL or blood eosinophil count < 140 cells/μL
3. $FE_{NO:}$ high versus low determined by median
4. Serum periostin level: high versus low determined by median level
5. Current post-BD FEV_1 reversibility defined as a post-BD change in FEV_1 of ≥ 12% and ≥ 200 mL demonstrated at one of the screening visits (Visit 1 [Week -5], Visit 2 [Week -4], or Visit 3 [Week -1])
6. Allergic versus non-allergic
7. Study sites: non-Japanese versus Japanese
8. ICS dose level: medium versus high

In addition to the 250 cells/μL cutoff for blood eosinophils, blood eosinophil counts as a continuous variable will be explored to differentiate between a responder and non-responder population. One blood eosinophil count cutoff may be selected for the Phase 3 eligibility criterion based on the treatment effect. Additional analyses on secondary endpoints and safety may be conducted based on the selected cutoff.

Analyses of the following subgroup populations of interest may also be conducted:

1. Gender: male versus female
2. Race: White versus non-White
3. Maintenance OCS use at screening: presence versus absence
4. $FE_{NO:}$ ≥ 24 ppb versus < 24 ppb (Hanania et al, 2013; Dweik et al, 2011)
5. Number of prior asthma exacerbations in the past year: 2 versus ≥ 3
6. Geographical region: North America/Western EU versus rest of world

Safety data will not be analyzed separately by subgroup.

4.8.4 Patient-reported Outcomes

Asthma Control Questionnaire-6

Asthma control will be evaluated by ACQ-6. The change from baseline in the mean ACQ-6 score will be analyzed. The proportion of subjects with change from baseline in the mean ACQ-6 score ≥ 0.5 during the study and the proportion of subjects who are well controlled (mean ACQ-6 score of ≤ 0.75), partially controlled (0.75 < mean ACQ-6 score ≤ 1.5), and uncontrolled (mean ACQ-6 score >1.5) will be compared between the individual MEDI9929 group and placebo group using the Fisher's exact test. A stratified log-rank test will be conducted to compare the time to first asthma control defined as a reduction from baseline in the mean ACQ-6 score ≥ 0.5 is first observed and the time to first partially control (0.75 < mean ACQ-6 score ≤1.5) and well controlled (mean ACQ-6 score of ≤ 0.75).

Asthma Daily Diary

Each item of the Asthma Daily Diary will be summarized showing change over time compared to baseline scores. Baseline will be defined as the 14-day period prior to dosing on Day 1 (ie, Day -15 to Day -1). Asthma Daily Diary data will be summarized as biweekly (14 day) means post dosing on Day 1. The change from baseline in the following endpoints will be analyzed:

- The mean symptom scores for daytime severity, daytime frequency, nighttime severity, and overall symptom score, where overall symptom score is the average of scores of daytime severity, daytime frequency, and nighttime severity
- The mean scores for the activity limitation questions
- Number of times rescue medication is used: daytime use, nighttime use, total rescue medication use (daytime + nighttime)
- The proportion of nights without nocturnal awakening and the proportion of nights without asthma-related nocturnal awakening (no awakening or wakening without rescue medication use)

4.8.4.1 Analysis of AQLQ(S)+12

The overall and 4 domain scores (symptoms, activity limitations, emotional function, and environmental stimuli) from the AQLQ(S)+12 responses along with their respective changes from baseline will be summarized using descriptive statistics. The change from baseline in the overall AQLQ(S)+12 score will be analyzed. Additionally, the proportion of AQLQ(S)+12 responders will be reported; subjects with ≥ 0.5 improvement and subjects

with ≥ 1.5 improvement from baseline in AQLQ(S)+12 scores at each visit will be reported separately.

4.8.4.2 Analysis of EQ-5D-5L

The responses from each dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the visual analog scale will be summarized by treatment group and visits. The shift tables will be provided for each dimension. The change from baseline in visual analog scale will be summarized with descriptive statistics by visit.

4.8.5 Safety

This will be assessed by summarizing AEs and SAEs using the as-treated population. Other variables used for the safety assessments include but are not limited to ECG, vital signs, and routine laboratory assessments, which will be evaluated in the MEDI9929 and placebo groups as changes from baseline. These variables as well as their changes from baseline will be summarized descriptively. In addition, shift tables will be included.

4.8.5.1 Analysis of Adverse Events

The occurrence of both treatment-emergent and non-treatment-emergent AEs and SAEs will be described by system organ class (SOC), preferred term, severity, and relationship to the investigational product. Related TEAEs/TESAEs are those events in which the investigator has assessed the relationship to investigational product as related. Subjects will be counted only once for each preferred term, once for each SOC, and by the highest severity of an event, regardless of how many instances of that event the subject experienced. Number of subjects with elevated liver function tests that meet the Hy's law definition will be summarized and evaluated. Verbatim terms will be coded to a standardized preferred term using the Medical Dictionary for Regulatory Activities, the AE classification dictionary endorsed by ICH.

4.8.5.2 Analysis of Clinical Laboratory Parameters

Hematology, serum chemistry, and urinalysis parameters (see Section 4.3.4) as well as their toxicity grade will be summarized with descriptive statistics by treatment group and visit. A shift table will also be provided for these clinical laboratory parameters by treatment group and visit.

4.8.5.3 Analysis of Electrocardiograms

The number of subjects with clinically significant abnormal ECG results based on investigators' judgments will be summarized by treatment group and visit for all subjects.

For the ECG sub-study (approximately 160 subjects), the 12-lead ECG results, QTc intervals (millisecond), will be summarized descriptively by treatment group and visit. Changes from baseline will be summarized into 3 categories: increase ≤ 30 millisecond, 30 millisecond < increase ≤ 60 millisecond, and increase > 60 millisecond by treatment group and visit. On Day 1, ECGs will be performed in triplicate; the average of these 3 reads will be used as baseline value. Shift tables for QTc intervals (QTc ≤ 450 millisecond, 450 < QTc ≤ 480 millisecond, 480 millisecond < QTc ≤ 500 millisecond, QTc > 500 millisecond) will be presented to compare the baseline ECG evaluation and the post-dose evaluations.

4.8.5.4 Analysis of Vital Signs

Vitals signs will be summarized by treatment group and visit. Pre-dose vital sign change from baseline to post-dose evaluations will also be summarized by treatment group and visit.

4.8.6 Analysis of Pharmacokinetics and Immunogenicity

MEDI9929 serum concentrations will be tabulated by treatment group along with descriptive statistics. Mean and individual serum MEDI9929 concentration-time profiles by treatment group will be plotted. Population PK modeling may be performed to better characterize the PK of MEDI9929 given by SC injection in asthmatic subjects. Potential correlation between PK exposure and PD biomarker, efficacy/safety response may be evaluated.

The incidence rate of positive antibodies to MEDI9929 will be reported by treatment group. If there is a high incidence of ADA, the association of ADA with MEDI9929 concentration will be assessed. In addition, the relationship between ADA and PD, efficacy, and safety may be evaluated.

4.8.7 Stage I, Stage II and Interim Analyses

Two formal analyses (Stage I analysis and Stage II analysis) and an interim analysis are planned for the study.

The Stage I analysis will be conducted after approximately 552 subjects have completed the Week 52 visit. During the Stage I analysis, all the efficacy and safety data collected through Week 52 will be analyzed. Study site personnel and the subjects will remain blinded to the treatment assignment until the end of follow-up period (Week 64). The primary analysis for which the study is powered will be completed in the Stage I analysis, and no new analyses based on primary efficacy endpoint will be made at the end of the study. Therefore, no further multiplicity adjustment will be applied.

The Stage II analysis for long-term safety follow-up will be performed after all subjects have completed the study (Week 64). Annualized asthma exacerbation and severe asthma exacerbation data along with other secondary endpoints measured through Week 64 will be analyzed.

It is anticipated that sites in Japan will randomize approximately 15% of the targeted enrollment of 552 subjects. In the event that enrollment of the Japanese subjects is delayed, and to ensure a timely Stage I analysis, non-Japanese sites may be permitted to continue to enroll subjects to reach the required sample size for the Stage I analysis. In this event, sites in Japan may continue to enroll until such time as approximately 15% of the targeted enrollment of 552 subjects has been enrolled while non-Japanese sites will be closed. Subgroup analysis of the Japanese subjects for the Stage I analysis will be conducted with available Japanese subjects who have completed the Week 52 visit.

There will be an interim analysis after approximately 552 subjects have completed the Week 28 visit. All data available at that time would be analyzed as part of the interim analysis. The objective of this interim analysis is to accelerate decisions on future development options for MEDI9929. Regardless of the interim analysis results, the study will be continued and completed. As a result, no alpha will be spent at the interim analysis. The interim analysis result may be used to accelerate planning for subsequent studies. Details related to unblinding for the interim analysis are in Section 4.6.2.3.

4.8.8 Data and Safety Monitoring Board

An independent DSMB will perform evaluations of safety data at specified regular intervals throughout the study and make recommendations to the sponsor regarding further conduct of the study. Information regarding unblinding for DSMB members is in Section 4.6.2.4. After reviewing the data by treatment group, the DSMB may request that a treatment group be unblinded for additional review. The DSMB does not include any investigators in this clinical study, and will include 4 voting members, 3 of whom are physicians with experience in respiratory diseases and in the diagnosis and management of asthma and 1 biostatistician. Specific details about the DSMB will be included in an external charter.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

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

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

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

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

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

  Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an ED or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse. In addition, any event of confirmed TB that requires treatment (inpatient or outpatient treatment by a health care provider) should be considered an SAE and reported to MedImmune Patient Safety (see Section 5.5).

For this study, AESIs that require rapid reporting (see Section 5.5) include anaphylactic reactions (see Appendix 2 for guidance for anaphylaxis diagnosis), confirmed immune complex disease (Type III hypersensitivity reactions), and malignancy. The rapid reporting of AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product.

5.3 Definition of Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious.

For this study, AESIs that do not require rapid reporting (see Section 5.4.3) include helminth infections, serious infections with special attention to respiratory infections, and injection site reactions that are not considered TESAEs. These AEs should be recorded in the eCRF once a diagnosis is confirmed, and will require additional data collection on the eCRF, but will not require rapid communication to MedImmune.

5.4 Recording of Adverse Events

Adverse events will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to MedImmune Patient Safety. See Section 5.2 for the definition of SAEs and Appendix 4 for guidelines for assessment of severity and relationship. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

5.4.1 Time Period for Collection of Adverse Events

Adverse events and SAEs will be collected from time of signature of informed consent throughout the treatment period, and including the follow-up period at Visit 32 (Week 64).

5.4.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.4.3 Recording of Helminth Infections, Serious Infections with Special Attention to Respiratory Infections, and Injection Site Reactions

Helminth infections, serious infections with special attention to respiratory infections, and injection site reactions (non-TESAEs) are AESIs that do not require immediate reporting. These AEs will require additional data collection on the eCRF, but do not require rapid reporting to MedImmune.

5.4.4 Reporting of Laboratory Abnormalities

Laboratory test results will appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable.

Any laboratory test result abnormality that fulfills the criteria for an SAE should be reported as such in addition to being recorded as an AE in the eCRF.

Any treatment-emergent abnormal laboratory test result that is clinically significant; ie, meeting 1 or more of the following conditions, should be recorded as a single diagnosis on the AE page in the eCRF:

- Accompanied by relevant clinical symptoms. For example, decreased white blood cell count accompanied by a suspicious infection, but not if accompanied by only a mild headache.
- Requiring corrective treatment/intervention
- Leading to a change in study medication; ie, dose is held or discontinued
- Requiring a change in concomitant therapy

Abnormalities that are Grade 3 or higher (according to the Common Terminology Criteria for Adverse Events, version 4.03 [CTCAE v4.03]) need to be queried and evaluated by the investigator to ensure that they do not meet the criteria for an AE.

This applies to any protocol and non-protocol specified safety laboratory test results that fall outside the laboratory reference ranges and meet the criteria above.

This does not apply to any abnormal laboratory test results that fall outside of the laboratory reference ranges, but do not meet the clinical significance criteria, as these will be analyzed and reported as laboratory abnormalities.

5.5 Reporting of Serious Adverse Events

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

MedImmune contact information:

Patient Safety
MedImmune
One MedImmune Way
Gaithersburg, MD 20878 USA
Fax: 1-301-398-4205

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

Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document

the event before notifying MedImmune Patient Safety of an SAE. When additional information becomes available, investigators should submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Patient Safety within 24 hours of learning of the new information.

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

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

Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 5.5 for contact information). If the overdose results in an AE, the AE must also be recorded on the AE eCRF (see Section 5.4). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 5.4 and Section 5.5). MedImmune does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

5.6.2 Hepatic Function Abnormality

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

In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event.

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

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

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

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

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

5.6.3 Pregnancy

Pregnancy in a female subject who has received investigational product is required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 5.5 for contact information).

Subjects who become pregnant during the study period must not receive additional doses of investigational product and will be withdrawn from the study. If the subject requests to know which treatment she received, this information will be provided to her. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to MedImmune Patient Safety after outcome.

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

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

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

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

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

6.2 Monitoring of the Study

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

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

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

6.2.1 Source Data

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

6.2.2 Study Agreements

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

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

6.2.3 Archiving of Study Documents

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

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through their last protocol-specified visit/assessment, regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.1.5 and Section 4.1.6).

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

6.4 Data Management

Data management will be performed according to the Data Management Plan.

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

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

6.5 Medical Monitor Coverage

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

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Ethical Conduct of the Study

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

7.2 Subject Data Protection

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

MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a MedImmune medical monitor or an investigator might know a subject's identity and also have access to his or her genetic data. Also regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

7.3 Ethics and Regulatory Review

An IRB/IEC should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The

investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff.

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

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

MedImmune or delegate should approve any modifications to the ICF that are needed to meet local requirements.

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

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

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

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

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

7.4 Informed Consent

The Principal Investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study

- Ensure the original, signed ICFs is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC

7.5 Changes to the Protocol and Informed Consent Form

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

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

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

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

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

7.6 Audits and Inspections

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

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9 SUMMARY PROTOCOL AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

Protocol Amendment 3, 01Aug2016

The purpose of this amendment is to change the Medical Monitor of the study. The major changes to the protocol are described below:

Title Page (Medical Monitor): Updated the title page of this protocol amendment to include the name, degree, and contact information of the new Medical Monitor, [redacted].

Protocol Amendment 2, 10Feb2016

The purpose of this amendment is to change the Medical Monitor of the study. The major changes to the protocol are described below:

Title Page (Medical Monitor): Updated the title page of this protocol amendment to include the name and contact information of the new Medical Monitor, [redacted].

Protocol Amendment 1, 15Oct2014

The original protocol was amended to modify several inclusion and exclusion criteria for ease of enrollment, to provide further clarification, and to correct typographical errors. The major changes and revisions to the protocol are incorporated into the body of Protocol Amendment 1 as described below.

1. **Section 1.4 (Summary of Clinical Experience):** Text was revised to update information for Study 20101183, which has now been completed.
2. **Section 1.6.2 (Secondary Hypotheses):** Hypothesis #2 was revised to correct the screening total serum IgE level from ≥ 100 IU/mL to > 100 IU/mL.
3. **Section 3.1.1 (Overview):** Text was revised that at least 50% of subjects will be currently reversible to allow more than 50% of currently reversible subjects to be enrolled into the study, which would represent more than half of the study population as defined by Inclusion Criterion #4.
4. **Section 4.1.2 (Inclusion Criteria):** Inclusion Criterion #6 was revised to allow subjects who have been on ICS/LABA for 6 months prior to Visit 1 and on a stable dose for 15 days prior to Visit 1 to enroll. The criterion was revised to ease enrollment by allowing 6 months instead of 12 months of inhaler use and decreasing the stable dose to 15 days prior to Visit 1 as 6 months of a stable asthma controller regimen is adequate to determine clinical response.
5. **Section 4.1.2 (Inclusion Criteria):** Inclusion Criterion #7 was revised to change the period in which subjects must be on stable controller medications from 30 to 15 days for consistency with other criteria.

6. **Section 4.1.2 (Inclusion Criteria):** Inclusion Criterion #11 was revised to add that subjects could have a documented history of at least 1 severe asthma exacerbation resulting in hospitalization (admission to the hospital for at least 24 hours) within the 12 months prior to Visit 1 as an alternative to at least 2 asthma exacerbation events. This addition will allow subjects with severe exacerbations resulting in hospitalization to participate in the study and ensure enrolling the most severe subjects. Additionally, text was added to clarify that to qualify as an asthma event an exacerbation resulting in an ED visit must require the use of systemic corticosteroids for at least 3 consecutive days.
7. **Section 4.1.3 (Exclusion Criteria):** Exclusion Criterion #3 was revised to exclude subjects who had been previous smokers but had stopped smoking for at least 6 months instead of 1 year to enroll. This criterion was revised to ease enrollment for subjects who were previous smokers but otherwise qualified for the study; smoking cessation for 6 months is clinically acceptable for eligibility. Exclusion Criterion #4 was revised from 30 days to 15 days for consistency.
8. **Section 4.1.3 (Exclusion Criteria):** Exclusion Criterion #9 was revised to exclude subjects who required antibiotics or antiviral medications for acute upper or lower respiratory infections to enroll if they received antibiotics or antivirals within 15 days instead of 30 days prior to Visit 1. This change was made to ease enrollment; completion of such treatment 15 days prior to enrollment is safe and clinically acceptable.
9. **Section 4.1.3 (Exclusion Criteria):** Exclusion Criterion #12 was revised to add text to the second bullet point for clarification that prophylaxis would be required only if TB positive.
10. **Section 4.1.3 (Exclusion Criteria):** Exclusion Criterion # 22 was revised to remove reference to live or live attenuated vaccine and create a new criterion.
11. **Section 4.1.3 (Exclusion Criteria):** Exclusion Criterion #30 was added to exclude any subject who received any oral or ophthalmic β-adrenergic antagonists (eg, propranolol) within 15 days prior to Visit 1 (Week -5). This criterion was added for consistency with medications listed as prohibited during the study.
12. **Section 4.1.3 (Exclusion Criteria):** Exclusion Criterion #31 was added to exclude any subject who received the Th2 cytokine inhibitor suplatast within 15 days prior to Visit 1 (Week -5).
13. **Section 4.1.3 (Exclusion Criteria):** Exclusion Criterion #32 was added to exclude any subject who received any live or attenuated vaccines within 15 days prior to Visit 1 (Week -5). This criterion was added for consistency with medications listed as prohibited during the study.
14. **Section 4.2.1 (Enrollment/Screening Period):** Text was added that permission to rescreen more than 1 time may be granted in the presence of extenuating circumstances and only with prior approval of the medical monitor. This text was added to allow for flexibility of additional screening upon review and approval of the medical monitor.
15. **Table 4.2-1 (Schedule of Screening Procedures**): Table was revised to amend footnote "a" to a minimum of 5 days between Visits 3 and 4, and to add + 2 days visit window to Visit 1. Footnote "a" was revised to correct the visit numbers; and the + 2 days visit window was added to Visit 1 to allow for a window to perform spirometry if prohibited medications have been taken.

16. **Table 4.2.2-1 (Schedule of Treatment Period Study Procedures – Week 0 to Week 24):** Table was revised to add footnote "e," there must be ≥ 7 days between doses. Footnote "e" was added to provide guidance regarding the amount of time between each dose of investigational product.
17. **Table 4.2.2-2 (Schedule of Treatment Period Study Procedures – Week 26 to Week 52):** Table was revised to add footnote "e," there must be ≥ 7 days between doses. Footnote "e" was added to provide guidance regarding the amount of time between each dose of investigational product.
18. **Section 4.2.3 (Follow-up Period), Order of Assessments, and Section 4.3.1.3 (Spirometry):** Text for Step 13 was revised to change the timing for spirometry testing to between 0600 and 1200 and that after the first screening spirometry at Visit 1, every effort should be made to conduct the spirometry testing at the same time that the first spirometry testing was done. This change was made to further clarify the spirometry procedure and to add an additional hour for initiation of testing.
19. **Section 4.3.1.3 (Spirometry), Post-bronchodilator Assessment:** Text was revised to add post-BD maneuvers with number of puffs used at baseline to identify the maximal post-BD FEV_1 measurement. This text was added to provide clarification regarding the number of post-BD maneuvers required during the study.
20. **Section 4.3.1.3 (Spirometry), Post-bronchodilator Assessment:** Text was changed from doses to puffs for Steps 2, 4, and 7 to provide clarification between the words "dose" and "puffs." The word "increase" was added to > 5% to the second bullet point in Step 9 to clarify the incremental change needed for additional spirometry at baseline.
21. **Section 4.3.4.1 (Tuberculosis Testing):** Text was revised to remove reference to repeat QFT-G test at least once during the screening period. This change was made because a repeat test during screening is unlikely to provide any new or additional information about a subject's TB status. The inclusion/exclusion criteria, in addition to the scheduled retesting during the study for subjects with an indeterminate QFT-G test result at screening, are sufficiently robust to determine a subject's TB status.
22. **Section 4.3.6 (Immunogenicity Evaluation and Methods):** Text stating that tiered analyses would be performed to evaluate ADA by screening and confirmatory assay was removed. This change was made because the ADA assay being employed is quantitative (ie, a sample will be either ADA negative or positive) and not qualitative (it is not a tiered assay). Using the term "tiered assay" suggests that the ADA assay being used is tiered; this change removes the possibility of ambiguity.
23. **Section 4.5.1.1 (Investigational Product Dose Preparation), Dose Preparation Steps:** Text was revised to change duration for thawing the investigational product from 1 - 2 hours to up to 2 hours. This change was made because the investigational product may be fully thawed prior to 1 hour; if that occurs, the investigational product can be prepared for administration.
24. **Section 4.5.1.3 (Monitoring of Dose Administration):** Text was revised to limit monitoring subjects post dose administration for a minimum of 2 hours to the first 2 doses and a minimum of 1 hour for the third and subsequent doses. This change was made because postdose reactions have not been observed in previous studies, so the follow-up period is being adjusted to reflect post-monitoring requirements.

25. **Section 4.7.1 (Permitted Concomitant Medications):** Text was revised to remove transfusions of blood and blood products during the study because blood products are considered prohibited concomitant medications.
26. **Section 4.7.2 (Prohibited Concomitant Medications):** Text was revised to add Th2 cytokine inhibitor (suplatast) to the list of medications considered exclusionary and not permitted during the study. Suplatast was added because the medication is available in some countries.
27. **Section 4.8.1 (General Considerations):** Text for the ITT population was revised for clarification and alignment with the statistical analysis plan to read, that the ITT population is defined as all subjects who are randomized and receive any investigational product.
28. **Section 4.8.4 (Patient-reported Outcomes), Asthma Daily Diary:** Text was revised to redefine baseline as the 14-day period prior to dosing on Day 1 and to add that the Asthma Daily Diary data will be summarized as biweekly (14-day), meaning post dosing on Day 1. Subsequent text was removed. The baseline and follow-up periods were changed from 7 to 14 days to more closely match the visit schedule. Additionally, text was added to the fourth bullet point to clarify that the proportion of nights without asthma-related nocturnal awakening means “no awakening or wakening without rescue medication use” for purposes of analysis.
29. **Section 4.8.8 (Data and Safety Monitoring Board):** Text was revised to change the number of DSMB voting members from 3 to 4, with 3 members to be physicians with experience in respiratory diseases and in the diagnosis and management of asthma, and 1 independent biostatistician. This change was made because recently updated MedImmune DSMB policy requires including an independent biostatistician as a voting member.
30. **Section 5.2 (Definition of Serious Adverse Events):** Text was added that AESIs that will require rapid reporting are to include anaphylactic reactions, confirmed immune complex disease, and malignancy, and to clarify that the rapid reporting of AESIs allows ongoing analysis of these events to characterize and understand them in association with the use of the investigational product. This text was moved from Section 5.3 (Definition of Adverse Events of Special Interest) to provide additional clarification regarding the need and reason to rapidly report AESIs of anaphylaxis, immune complex disease, and malignancy as SAEs.
31. **Section 5.3 (Adverse Events of Special Interest) and Section 5.4.3 (Recording of Helminth Infection and Injection Site Reactions):** Text and section heading were revised to add serious infections with special attention to respiratory infections as it is listed as a potential risk in the development Risk Management Plan.
32. **: Section 5.4.4 (Reporting of Laboratory Abnormalities):** This section was added to provide additional guidance to investigators for reporting clinically significant laboratory test abnormalities and the conditions in which they should be reported as AEs or SAEs.

Appendix 1 Signatures

Sponsor Signature(s)

A Phase 2 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI9929 in Adult Subjects with Inadequately Controlled, Severe Asthma

I agree to the terms of this protocol amendment.

Signature and date: electronic signature appended

[redacted]
One MedImmune Way, Gaithersburg MD, 20878, USA
Telephone number: [redacted]

Signature of Principal Investigator

A Phase 2 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI9929 in Adult Subjects with Inadequately Controlled, Severe Asthma

I, the undersigned, have reviewed this protocol, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available)_____

Appendix 2 National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) Guidance for Anaphylaxis Diagnosis

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

NIAID and FAAN define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

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

   AND AT LEAST ONE OF THE FOLLOWING

   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEFR, 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 patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEFR, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that subject (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

Appendix 3 Signs and Symptoms and Management of Acute Anaphylaxis

Signs and Symptoms of Acute Anaphylaxis

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

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

Other earlier or concomitant signs and symptoms can include:

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

Management of Acute Anaphylaxis

I. Immediate intervention

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

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

a. Place patient in recumbent position and elevate lower extremities.
b. Establish and maintain airway.
c. Administer oxygen.
d. Establish venous access.
e. Normal saline IV for fluid replacement.

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

a. Consider epinephrine infusion.
b. Consider H1 and H2 antihistamines.
c. Consider nebulized β2 agonist (eg, albuterol [salbutamol]) for bronchospasm resistant to epinephrine.
d. Consider systemic corticosteroids.
e. Consider vasopressor (eg, dopamine).
f. Consider glucagon for patient taking b-blocker.
g. Consider atropine for symptomatic bradycardia.
h. Consider transportation to an emergency department or an intensive care facility.
i. For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary.

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

Appendix 4 Additional Safety Guidance

Assessment of Severity

The severity definitions below are from Clinical Data Interchange Standards Consortium. (CDISC) Version 3.1.1.

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

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

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of Relationship

Relationship to Investigational Product

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

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

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

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

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

Relationship to Protocol Procedures

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

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

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

Appendix 5 Estimated Equipotent Daily Doses of Inhaled Glucocorticosteroids for Adults

Drug	Medium Daily Dose (µg)	High Daily Dose (µg)
Beclomethasone dipropionate - CFC	> 500 - 1000	> 1000 to 2000
Beclomethasone dipropionate - HFA	> 250 - 500	> 500
Budesonide	> 400 - 800	> 800-1,600
Ciclesonide	> 160 - 320	> 320-1,280
Flunisolide	> 1000 - 2000	> 2000
Fluticasone propionate	> 250 - 500	> 500 1000
Mometasone furoate	> 400 - 800	> 800
Triamcinolone acetonide	> 1000 - 2000	> 2000

CFC = chlorofluorocarbon; HFA = hydrofluoroalkane

Adapted from Pocket Guide for Asthma Management and Prevention. Global Initiative for Asthma (GINA). Available from www.ginasthma.org. Updated 2012.

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[redacted]	Clinical Approval	01-Aug-2016 19:04 GMT+010
[redacted]	Nonclinical Scientist Approval	02-Aug-2016 13:45 GMT+010
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