A Phase 2a, Double-blind, Placebo-controlled Study to Evaluate the Efficacy of MEDI-563 in Subjects with Moderate-to-severe Chronic Obstructive Pulmonary Disease and Sputum Eosinophilia

Sponsor Protocol Number: MI-CP196 (D3251L00001)

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Investigational Product: MEDI-563, a humanized anti-IL-5 receptor alpha chain antibody

Sponsor: MedImmune Limited, an affiliate of AstraZeneca AB

Medical Monitor: [redacted]
Phone: [redacted];
Fax: [redacted]

Protocol History, Date: Original Protocol, 22Jul2010
Protocol Administrative Change 1, 13Oct2010
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Sponsor Agreement:

I, the undersigned, am authorized to sign the protocol on behalf of the sponsor.

Medical Monitor Signature _____ Date _____

Medical Monitor Name _____
(please print)

Investigator Agreement: MI-CP196

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.

Investigator Signature _____ Date _____

Investigator Name and Title _____
(please print)

Investigator Affiliation, City, State/Province_____

_____
(please print)

Site/Center Number (if available) _____

Table of Contents

List of In-text Tables

List of In-text Figures

List of Appendices

List of Abbreviations

Abbreviation or Specialized Term	Definition
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AECOPD	acute exacerbations of COPD
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
BHR	bronchial hyperresponsiveness
BMI	body mass index
BODE	Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity
CGI	Clinicians Global Impression
CI	confidence interval
CMH	Cochran-Mantel-Haenzel
COPD	chronic obstructive pulmonary disease
CPK	creatinine phosphokinase
CPK-MB	creatinine phosphokinase isoform MB
CRO	Contract Research Organization
CRP	c-reactive protein
CRPS	Clinical Research Pharmacy Service
CRQ	Chronic Respiratory Questionnaire
CRQ-SAS	Chronic Respiratory Questionnaire self-administered standardized format
CT	computed topography
DLCO	diffusion capacity of carbon monoxide
ECG	electrocardiogram
ECP	eosinophil cationic protein
eCRF	electronic case report form
eDiary	electronic diary
EDN	eosinophil derived neurotoxin
EMEA	European Medicines Agency
EU	European Union
ERS	European Respiratory Society
EXACT-PRO	EXAcerbations of Chronic pulmonary disease Tool - Patient Reported Outcome

Abbreviation or Specialized Term	Definition
FDA	Food and Drug Administration
FEIA	fluorescence enzyme immunoassay
FEV_1	forced expiratory volume in 1 second
FeNO	fractional exhaled nitric oxide
FRC	functional residual capacity
FVC	forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative For Asthma
HEENT	head, ears, eyes, nose, throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQOL	health related quality of life
HRU	health resource utilization
IC	inspiratory capacity
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IL-5	interleukin-5
IL-5Rα	interleukin-5 receptor alpha subunit
IM	immunogenicity
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-Treat
IV	intravenous
IXRS	interactive voice/web response system
5-LO inhibitors	5-lipoxygenase inhibitors
LTOT	long-term oxygen therapy
MBP	major basic protein
MOV	maximum observed value
MMRC	Modified Medical Research Council

Abbreviation or Specialized Term	Definition
6MWT	6 Minute Walk Test
NO	nitric oxide
NK	natural killer (cells)
O_2	oxygen
OLD	obstructive lung disease
PD	pharmacodynamics
PDA	personal digital assistant
PEF	peak expiratory flow
PP	Per-Protocol
PK	pharmacokinetics
RNA	ribonucleic acid
RT-PCR	reverse transcriptase polymerase chain reaction
RV	residual volume
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SGRQ-C	COPD-Specific Saint George's Respiratory Questionnaire
SMC	Safety Monitoring Committee
SpO_2	oxygen saturation
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TLC	total lung capacity
US	United States
VAS	visual analogue scales
VC	vital capacity
WBC	white blood cell

Study Abstract

TITLE

A Phase 2a, Double-blind, Placebo-controlled Study to Evaluate the Efficacy of MEDI-563 in Subjects with Moderate-to-severe Chronic Obstructive Pulmonary Disease and Sputum Eosinophilia

OBJECTIVES

Primary Objective

The primary objective of this study is to evaluate the effect of multiple subcutaneous (SC) doses of MEDI-563 on the rate of moderate-to-severe acute exacerbations in chronic obstructive pulmonary disease (AECOPD) in adult subjects with moderate-to-severe COPD who exhibit eosinophilia (≥ 3.0% sputum eosinophilia in the previous 12 months or at screening) in sputum compared to placebo.

Secondary Objectives

The secondary objectives of this study are:

1) To evaluate the safety and tolerability of MEDI-563 in this subject population
2) To evaluate the reduction in hospitalizations due to AECOPD
3) To assess the effect of MEDI-563 on health-related quality of life measurements such as the chronic obstructive pulmonary disease (COPD)-specific Saint George's Respiratory Questionnaire (SGRQ-C) and the Chronic Respiratory Questionnaire self-administered standardized format (CRQ-SAS)
4) To describe the effect of MEDI-563 on the BODE (Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity) index

Exploratory Objectives

The exploratory objectives of this study are:

1) To assess the effect of MEDI-563 on the time to first moderate-to-severe AECOPD
2) To assess the number of subjects who exhibit at least one moderate-to-severe AECOPD
3) To assess the effect of MEDI-563 on the number of exacerbation-free days as measured by the EXAcerbations of Chronic pulmonary disease Tool – Patient Reported Outcome (EXACT-PRO)
4) To assess the effect of MEDI-563 on the number, duration, and severity of moderate-to-severe AECOPD as measured by the EXACT-PRO
5) To assess the effect of MEDI-563 on pulmonary function as assessed by changes from baseline in forced expiratory volume in 1 second (FEV_1)
6) To describe the effect of MEDI-563 on functional performance, measured by 6 Minute Walk Test (6MWT)
7) To describe the pharmacokinetics (PK) and immunogenicity (IM) of MEDI-563 in COPD subjects
8) To assess the effect of MEDI-563 on dyspnea symptom as measured by the Modified Medical Research Council (MMRC) Dyspnea Scale
9) To assess the effect of MEDI-563 on symptom scores as measured by visual analogue scales (VAS). Symptom scores include cough, breathlessness, sputum purulence, and sputum production.
10) To assess the effect of MEDI-563 on the use of concomitant medications
11) To assess all-cause mortality in the 1 year post-randomization amongst all subjects randomized to

	treatment
12)	To evaluate the effect of MEDI-563 on blood and sputum biomarkers
13)	To assess the effect of MEDI-563 on healthcare resource utilization and economics
14)	To assess the effect of MEDI-563 on total serum immunoglobulin E (IgE) and IgE fluorescence enzyme immunoassay (FEIA) for common aeroallergens
15)	To develop and test clinical prediction rules (diagnostic tools) for discriminating COPD phenotypes

STUDY DESIGN

This is a Phase 2a, randomized, double-blind, placebo-controlled, multicenter study evaluating the effect of multiple SC doses of MEDI-563 on the rate of moderate-to-severe AECOPD in adult subjects with moderate-to-severe COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD; GOLD, 2009). Eligible subjects will have a documented history of AECOPD within 2 to 12 months prior to Day 1 and a sputum eosinophil count of ≥ 3.0% within 12 months prior to, or at screening.

Subjects will be screened between Day -56 and Day -29. Prior to randomization, all subjects will undergo a 28-day run-in period (Day -28 to Day -1), during which their current inhaled corticosteroids and/or long-acting β-agonist will be replaced with Symbicort® (budesonide/formoterol fumarate) 200/6 µg/inhalation: 2 inhalations twice daily if FEV_1 is < 50% predicted or Spiriva® (tiotropium bromide monohydrate) 18 µg/inhalation once daily if 50% ≤ FEV_1 < 80% predicted. The subjects will be provided with a short-acting β2-agonist for symptom relief during the study (terbutaline sulphate, Bricanyl®). Subjects who remain clinically stable during the 28-day run-in period and meet eligibility criteria will continue the maintenance treatment with Symbicort® or Spiriva® and may be randomized into the study to receive investigational product as an add-on therapy for 48 weeks. Approximately 90 subjects from multiple sites will be randomized in a 1:1 ratio to receive either 100 mg SC MEDI-563 or placebo. Investigational product (MEDI-563 or placebo) will be administered subcutaneously in an outpatient setting every 28 days for the first 3 doses and then every 56 days for the next 5 doses up to Day 337 (total 8 doses). Subjects will be followed for a total of 32 weeks (to Day 561). Post Day 561, subjects will continue until peripheral blood eosinophil counts return to 50 cells/µL or 20% of baseline.

Baseline measurements at screening will include evaluation of disease activity; pulmonary function tests (forced vital capacity [FVC], FEV_1); patient-reported outcomes (SGRQ-C, CRQ-SAS, MMRC dyspnea scale, EXACT-PRO, patient symptom scores [VAS]); analysis of eosinophil-generated proteins, sputum induction for analysis to include cell count and biomarkers; serology for parasites and stool sampling (if applicable); medical assessment; and pulse oximetry.

The following evaluations will be conducted during the course of the study. Evaluations will include assessments of disease activity; pulmonary function testing; analysis of eosinophil and basophil activation proteins; inflammation markers associated with COPD and the acute phase response, cytokines, tryptase, in serum and sputum; assessment of exacerbations; use of concomitant medications; patient-reported outcomes (SGRQ-C, CRQ-SAS, MMRC dyspnea scale, VAS symptoms, EXACT-PRO); functional assessment (6MWT); COPD severity (BODE index); safety assessments (adverse events [AEs] and serious adverse events [SAEs]); physical examination, vital signs, oxygen saturation, serum chemistry, hematology, urinalysis, PK and IM. Not all evaluations will be done at each visit.

Subject enrolment is anticipated to take approximately 12 months. Subjects will be in the study for approximately 88 weeks (up to 28 days for screening, 28 days run-in, up to 48 weeks [Day 1 to Day 337] of treatment, and 32 weeks of follow-up [to Day 561]).

SUBJECT POPULATION

The subjects in this study will be adult subjects aged 40-85 years with moderate-to-severe COPD as defined by GOLD (GOLD, 2009) who have a documented history of AECOPD within 2-12 months prior to screening and a sputum eosinophil count of ≥ 3.0% within 12 months prior to, or at screening.

TREATMENT

A total of 90 subjects will be randomized in a 1:1 ratio to receive either 100 mg of SC MEDI-563 or placebo. Investigational product (MEDI-563 or placebo) will be administered as an SC injection in the outpatient setting every 28 days for the first 3 doses and then every 56 days for the next 5 doses for a total of 8 doses to Day 337.

In addition, all subjects will receive Symbicort® 200/6 µg/inhalation: 2 inhalations twice daily if FEV_1 is < 50% predicted or Spiriva® 18 µg/inhalation once daily if 50% ≤ FEV_1 < 80% predicted as maintenance therapy starting on Day -28. Subjects will receive Bricanyl® as rescue medication.

ASSESSMENT OF ENDPOINTS

The primary objective of this study is to evaluate the effect of multiple SC doses of MEDI-563 on the rate of moderate-to-severe AECOPD in adult subjects with moderate-to-severe COPD. The primary endpoint will be the number of moderate-to-severe AECOPD experienced by subjects after their first dose of investigational product to their Day 393/Early Discontinuation visit.

A Van Elteren test will be performed for testing the differences in number of moderate-to-severe AECOPDs between the MEDI-563 treatment group and the placebo group. The Van Elteren test is a stratified Cochran-Mantel-Haenzel (CMH) Row Mean Scores test, which is the equivalent to Kruskal-Wallis test when the comparison is performed between the MEDI-563 treatment group and the placebo group without involving other stratification factor(s). The two-sided test will be conducted over the Per Protocol (PP) Population and will constitute the primary analysis for which this study is powered.

Adverse events and SAEs will be summarized categorically by system organ class, preferred term, severity, and relationship to investigational product. The number and proportion of subjects that are hospitalized due to moderate-to-severe AECOPD will be summarized by treatment group. The annual rate of hospitalization due to moderate-to-severe AECOPD may be compared between the MEDI-563 group and the placebo group using a Poisson regression model with an overdispersion parameter to adjust for variability in the data. A log-rank test will be conducted to compare the time to first moderate-to-severe AECOPD between the MEDI-563 group and placebo group. A proportional hazard model may be used to explore the effect of some covariates. The number and proportion of subjects who exhibit at least one moderate-to-severe AECOPD will be summarized by treatment group. The Fisher's exact test will be carried out to compare the proportion of subjects who exhibit at least one moderate-to-severe AECOPD between the MEDI-563 group and placebo group.

A summary of baseline score and changes from baseline will be performed for the SGRQ-C. The absolute change value as well as the proportion of subjects with a 4-point change (improvement), an 8-point change, and a 12-point change in total scores will be tabulated by treatment group. A summary of baseline score changes from baseline will be performed for the CRQ-SAS. The proportion of subjects with a 0.5-point change (improvement) in each dimension will be tabulated by treatment group.

Both Bode Index and MMRC scale will be tabulated by treatment group. A shift table may be produced.

PRIMARY EFFICACY ANALYSIS

The primary efficacy analysis will be conducted after all subjects who have either completed the Day 393 evaluations or have been discontinued from the study early. Since the primary endpoint analysis for which this study is powered will be completed at the primary efficacy analysis, it will not be repeated at the end of the study. As such there is no need for multiplicity adjustment of the Type I error. Analysis of safety data available at the time of data cut-off will be presented in the primary efficacy analysis. If necessary, analyses of limited secondary endpoints may be included in the primary efficacy analysis. The primary efficacy analysis methodology and the review of the resulting data within the Sponsor will be described in the statistical analysis plan. The actual data from the primary efficacy analysis will not be communicated to personnel at the contract research organization or investigational sites or to enrolled subjects.

SAMPLE SIZE AND POWER CALCULATIONS

Sample size and power calculations have been performed for the primary endpoint of moderate-to-severe

AECOPD rate to allow hypothesis testing. Sample size and power calculations are based on the Van Elteren test (two-sided) with alpha = 0.05 for testing the difference in moderate-to-severe AECOPD rates between the MEDI-563 treatment group (100 mg) and the placebo group. Assumptions include: (1) moderate-to-severe AECOPDs evaluated through Day 393 and (2) a MEDI-563 to placebo randomization ratio of 1:1.

With 72 subjects (n = 36 for MEDI-563 and n = 36 for placebo), the power to detect statistically significant differences in the moderate-to-severe AECOPD rates between the MEDI-563 treatment group and the placebo group is presented in ranges from 48.6% to 94.0%. The Van Elteren test is a stratified CMH Row Mean Score test. As there is no formal formula for calculating power using the CMH row mean score test, power calculations were performed using a simulation program.

Assuming a drop-out rate of about 20% in the study, a total of 90 subjects are needed for this study.

1 Introduction

AstraZeneca AB, a company incorporated in Sweden with offices at SE-151 85 Södertälje, Sweden ("AstraZeneca"), is the global sponsor of this study. MedImmune Limited, with offices at Milstein Building, Granta Park, Cambridge, CB21 6GH, UK ("MedImmune") and MedImmune, LLC with offices at One MedImmune Way Gaithersburg, MD 20872 USA, are affiliates of AstraZeneca. MedImmune, LLC is the sponsor representative in the US. In this study, MedImmune manages the duties and functions related to the development of the clinical protocol, Investigator's Brochure, supplying and handling of investigational products, safety information and data handling, and any other duties as agreed with AstraZeneca.

1.1 Disease Background

Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and mortality worldwide. In contrast to other chronic diseases, COPD is increasing in prevalence and is projected to be the third-leading cause of death and disability worldwide by 2020. The costs to society for treating COPD are high, accounting for approximately 3.4% of the total health care budget of the European Union (EU). In the United States (US), the direct and indirect costs of COPD are estimated to be more than $30 billion (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2009).

Acute exacerbations of COPD (AECOPD) are responsible for a large portion of the economic burden of COPD. An AECOPD is defined as a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD (Rodriguez-Roisin, 2000).

More than 500,000 hospitalizations and 100,000 deaths are attributed to AECOPD in the US each year (Owings and Lawrence, 1997; Hoyert et al, 1999) and their exact causes (viral, bacterial, pollutants, etc.) are difficult to ascertain. Direct costs for AECOPD were more than $18 billion in the US in 2002 (Anzueto et al, 2007). In addition to a substantial economic burden, AECOPD is also responsible for much of the morbidity and mortality from COPD. Patients with frequent AECOPD are associated with increased inflammation and accelerated decline in lung function as compared to patients with infrequent exacerbations (Donaldson et al, 2002). In the hospital, mortality for AECOPD remains high at approximately 10% (GOLD, 2009). Risk for relapse and readmission after hospital discharge for AECOPD

continues to be high and mortality rates at 1 year from the index admission have been reported at 43% (Connors et al, 1996).

1.2 Description of MEDI-563

MEDI-563 is a humanized, afucosylated monoclonal antibody that specifically binds to the human interleukin-5 receptor alpha subunit (IL-5Rα). The interleukin-5 (IL-5) receptor is a heterodimer consisting of an alpha and a beta chain. The alpha chain is shared among eosinophils, basophils, and cultured human mast cells (Dahl et al, 2004), and upon binding to the receptor, MEDI-563 triggers antibody-dependent cell-mediated cytotoxicity that leads to eosinophil apoptosis within 24 hours of intravenous (IV) administration.

1.3 Rationale for Study Conduct

Approximately 30% of patients with COPD have elevated levels of eosinophils in the airway as measured by sputum induction or bronchoalveolar lavage (BAL; Brightling et al, 2000; 2005; Pizzichini et al, 1998; Leigh et al, 2006; reviewed in Saha and Brightling, 2006). In COPD, the response to oral and inhaled corticosteroids (ICS) is related to the intensity of the airway eosinophilic inflammation (Brightling et al, 2000; Brightling et al, 2005) and a sputum eosinophilia > 3% has been demonstrated to be a good predictor of response to steroids in COPD (Pizzichini et al, 1998; Leigh et al, 2006). A strategy in which increasing therapy with corticosteroids were used to control sputum eosinophilia > 3% in COPD resulted in a reduction in the frequency of severe COPD exacerbations requiring admission to a hospital when patients were stepped up to oral corticosteroid therapy (Siva et al, 2007). Standard therapy for AECOPD includes treatment of inflammation with systemic corticosteroids, which are associated with a reduction in length of hospital stay and hastened recovery (Cochrane review, 2005). Corticosteroids are responsible for early apoptosis of eosinophils and generally result in a reduction in eosinophilia. Long-term therapy with corticosteroids is unfortunately associated with significant side effects such as suppression of the hypothalamic-pituitary-adrenal axis and osteoporosis, and they do not avert exacerbations in all eosinophilic COPD patients (Siva et al, 2007). Therefore, a strategy that reduces eosinophilic inflammation without the corticosteroid-induced side effects is needed.

Siva et al (Siva et al, 2007) showed that a management strategy that aims to minimize eosinophilic airway inflammation and symptoms is associated with a significant reduction in the frequency of COPD exacerbations requiring hospital admission. The majority of this

benefit occurred in patients with significant eosinophilic airway inflammation. Recent evidence also indicates that COPD patients with increased sputum eosinophil counts had significant improvements in forced expiratory volume in 1 second (FEV_1) and quality of life-scores that were associated with decreased sputum eosinophil counts and eosinophil cationic protein (ECP) levels (Pizzichini et al, 1998). These data suggest that therapies specifically targeting eosinophils in COPD patients with elevated sputum eosinophil counts may have beneficial effects. Treatment options are limited in severe exacerbations of COPD and by depleting the eosinophil count in the periphery and sputum; MEDI-563 may be an alternative option for this high unmet need.

MEDI-563 is being developed for treatment of asthma, and this will be the first study with MEDI-563 in subjects with COPD. The purpose of this Phase 2a study is to investigate the efficacy of multiple 100 mg subcutaneous (SC) doses of MEDI-563 in adult subjects with moderate-to-severe COPD. The primary objective of this study is to evaluate the effect of MEDI-563 on the rate of moderate-to-severe AECOPD in adult subjects with moderate-to-severe COPD who exhibit eosinophilia (≥ 3.0% sputum eosinophilia in the previous 12 months or at screening) in sputum compared to placebo. The study is intended to provide efficacy and safety data to enable the progression of the clinical development program in COPD patients. In addition to the primary objective, the effects of MEDI-563 on validated COPD clinical outcomes and the pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity (IM) of MEDI-563 will be assessed in the COPD population.

1.4 Benefit-Risk and Ethical Assessment

Nonclinical pharmacology studies have shown that MEDI-563 binds to eosinophils through the IL-5Rα, and blocks the binding of the ligand, IL-5 to its receptor. This activates effector cells leading to antibody-dependent cellular cytotoxicity (ADCC), resulting in the destruction of eosinophils. Studies performed in a number of in vivo models of peripheral eosinophilia and allergic asthma demonstrated that MEDI-563 depletes eosinophils. Marked peripheral blood eosinophil depletion was observed in toxicology studies in cynomolgus monkeys following IV (9 weeks) and SC (16 weeks and 9 months) administration, and to a less extent, transient decreases in white blood cells (WBCs). High titers of anti-MEDI-563 antibody were seen in 1 of 24 animals following IV administration and in 2 of 36 animals following SC administration.

To mitigate the risk of prolonged eosinophil depletion caused by MEDI-563, peripheral blood eosinophils will be monitored throughout the study. This includes long-term follow-up after completion of the study (Day 561). If on Day 561, a subject's peripheral blood eosinophil count has not returned to 50 cells/µL or 20% of the Day 1 value, then the subject will be asked to return to the study site every 84 days until the subject's peripheral blood eosinophil count returns to 50 cells/µL or 20% of the Day 1 value.

A report in the literature showed that ablation of eosinophils with anti-IL-5 antibody in mice enhanced the survival of *Trichinella spiralis* (Vallance et al, 2000). On the other hand, depletion of eosinophils in other murine *Trichinella spiralis* infection models have shown no effect on the ability to clear parasitic infestations (Herndon and Kayes, 1992) and may even compromise parasite survival (Fabre et al, 2009). The importance of eosinophils in the control of parasitic infestations in humans is also uncertain. To mitigate the potential risks that may be associated with eosinophil depletion due to MEDI-563, subjects with any of the following characteristics will be excluded from participation in the study: 1) unexplained diarrhea within 30 days prior to screening; 2) diagnosis of helminth parasitic infection within 6 months prior to screening; 3) history of an untreated systemic helminth parasitic infestation; 4) history of living with a person known to have had a helminth parasitic infestation within 12 months prior to screening; 5) history of recent travel to areas where parasite infestations are endemic within 3 months before screening or 6) positive serum serology during the screening/run-in period to Strongyloides stercoralis, Schistosoma mansoni, Taenia solium or Ascaris lumbricoides (see Section 4.2.2). Because the sensitivity of stool evaluation for *Strongyloidiasis*, *Schistosomiasis* and *Cysticercosis* is relatively low (CDC, 2010) serum serologies for these parasites will be obtained during the screening/run-in period to maximize detection of these infestations. Any subjects with positive serology for *Schistosoma mansoni, Taenia solium or Ascaris lumbricoides* will undergo a confirmatory stool sampling per local guidelines. If the stool sampling is positive for *Schistosoma mansoni* or *Taenia solium* the subject will be excluded. All subjects with a positive serology for *Ascaris lumbricoides* will be treated with a single oral dose of 400mg albendazole. If albendazole is not licensed, the subject will be treated per local standard of care. Any subjects with positive Strongyloides stercoralis serology will be excluded (see Section 4.2.2).

Of the 4 clinical studies in development for asthma, 2 have completed (MI-CP158 and MI-CP197) and 2 are ongoing (MI-CP166 and MI-CP186). The first clinical study of MEDI-563 in humans was MI-CP158. MI-CP158 was a Phase 1, open-label, dose-escalation study evaluating the safety and tolerability of single IV doses of MEDI-563 in subjects with

mild asthma. In this study, subjects initially received escalating single IV doses of MEDI-563 from 0.03 to 3.0 mg/kg. A total of 44 subjects have received a single IV dose of MEDI-563 in this study. MEDI-563 was well tolerated in this study. The majority (86.5%) of adverse events (AEs) was mild in severity, and there were no deaths, serious adverse events (SAEs), severe AEs, or any AEs that resulted in MEDI-563 discontinuation. The most common AE was decreased WBC count (15/44 subjects, 34.1%), the severity of which was mild. Peripheral blood eosinophil suppression was observed following single IV dose administration of MEDI-563 at all dose levels, with persistent suppression observed at single IV doses of 0.03 mg/kg and higher. Reductions in mean ECP levels occurred immediately (Day 1) at all dose levels except the 3.0 mg/kg dose group, where reductions occurred at Day 2. In general, the reduction in mean ECP correlated with the peripheral blood eosinophil suppression observed across dose groups. Seven of 37 subjects (18.9%) had quantifiable (titer range 50-6400) anti-MEDI-563 antibodies some time during the course of the study. There appeared to be no relationship between the presence of anti-MEDI-563 antibody titers and the AEs experienced by these subjects during the study.

Study MI-CP197 was a Phase 2a, randomized, double-blind, placebo-controlled, dose-escalation, multicenter study evaluating the safety, tolerability, PK, and IM of multiple SC doses of MEDI-563 in adult subjects with asthma. Six subjects received placebo and 18 subjects received MEDI-563 (25, 100, or 200 mg) as SC injections on Days 0, 28, and 56; one additional subject received a single dose of MEDI-563 (25mg). A total of 7 subjects received the 25 mg dose and 6 subjects each received the 100-mg and 200-mg doses. MEDI-563 was well tolerated in this study. The majority (89.7%) of AEs across the MEDI-563 groups was mild or moderate in severity, and there were no deaths, SAEs, nor any AEs that resulted in MEDI-563 discontinuation. The most common AEs were upper respiratory infection, asthma, headache, and decreased WBC count. No dose effect was apparent in the incidence of AEs by preferred term across the MEDI-563 dose groups. Four of 19 subjects (21.0%) had quantifiable (titer range 50-3200) anti-MEDI-563 antibodies some time during the course of the study.

These previous clinical studies with MEDI-563 have provided safety and tolerability data for MEDI-563 when administered by both single and multiple IV infusion or SC injection. MEDI-563 appeared to be safe and well tolerated. Although COPD and asthma are 2 distinct conditions in terms of disease onset, frequency of symptoms and reversibility of airway obstruction, the 2 conditions have similar signs such as coughing and wheezing and are treated with similar medications. There is increasing scientific and clinical evidence that

asthma and COPD share many common origins (ie, epidemiologic characteristics and clinical manifestations), a theory that is known as the Dutch hypothesis (Orie et al, 1961) and recently reviewed by Postma et al (Postma et al, 2004). Their conclusions were based on a comparison of signs, laboratory findings, treatment responses, and natural history. The 3 components of this hypothesis are as follows: (1) various forms of obstructive lung disease (OLD) have overlapping clinical features, and defining the specific clinical phenotype with which to characterize obstructive airways disease (eg, symptoms, allergy, and bronchial hyperresponsiveness [BHR]) was proposed by Orie and coworkers; (2) one form of OLD (asthma) may evolve into another (COPD); and (3) the development of OLD is based on allergy (ie, inflammation) and BHR, and endogenous (host) factors determined by heredity (genes), but is modulated by exogenous (ie, environmental) factors (eg, allergens, infections, smoking, pollution, age, and airway geometry) (Orie et al, 1961; Silverman et al, 2002).

The first-line maintenance therapy for most patients with asthma is an ICS, with the addition of a bronchodilator if needed to control symptoms. However, the reverse is true for the treatment of COPD where bronchodilators are the first-line maintenance treatment. Combination therapy with both ICS and long-acting β2-agonist has recently been shown to be effective in COPD, where studies have documented additive improvement in FEV_1 (Kerstjens et al, 1992; Anthonisen et al, 1994; Burge et al, 2000). The most important finding in the ISOLDE study was that patients receiving ICS had fewer exacerbations (Burge et al, 2000). These results have led to a recommendation for the use of ICS in moderate-to-severe COPD to reduce exacerbations (Pauwels et al, 2001). Overall, the same therapeutic approaches show clinical effectiveness in both asthma and COPD. COPD patients with eosinophilic airway inflammation (sputum eosinophils > 3%) are more prone to severe exacerbation than patients with < 3% sputum eosinophils (Siva et al, 2007). These patients have shown an increased response to ICS compared with noneosinophilic COPD patients (Leigh et al, 2006). Hence, the response to and the safety profile of MEDI-563 should be similar in these 2 patient populations. As none of the existing drugs for the treatment of COPD has been shown to have a significant effect on the exacerbation rate and long-term decline in lung function, the projected benefits are significant and the risks likely to be rare and treatable. In addition to plans to manage these possible reactions, sites should have ready access to specialist advice. Nevertheless, every effort has been made to minimize risk to subjects participating in the proposed study.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to evaluate the effect of multiple SC doses of MEDI-563 on the rate of moderate-to-severe AECOPD in adult subjects with moderate-to-severe COPD who exhibit eosinophilia (≥ 3.0% sputum eosinophilia in the previous 12 months or at screening) in sputum compared to placebo.

2.2 Secondary Objectives

The secondary objectives of this study are:

1) To evaluate the safety and tolerability of MEDI-563 in this subject population
2) To evaluate the reduction in hospitalizations due to AECOPD
3) To assess the effect of MEDI-563 on health-related quality of life measurements such as the COPD-Specific Saint George's Respiratory Questionnaire (SGRQ-C) and the Chronic Respiratory Questionnaire self-administered standardized format (CRQ-SAS)
4) To describe the effect of MEDI-563 on the BODE (Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity) index

2.3 Exploratory Objectives

The exploratory objectives of this study are:

1) To assess the effect of MEDI-563 on the time to first moderate-to-severe AECOPD
2) To assess the number of subjects who exhibit at least one moderate-to-severe AECOPD
3) To assess the effect of MEDI-563 on the number of exacerbation-free days as measured by the EXAcerbations of Chronic pulmonary disease Tool – Patient Reported Outcome (EXACT-PRO)
4) To assess the effect of MEDI-563 on the number, duration, and severity of moderate-to-severe AECOPD as measured by the EXACT-PRO
5) To assess the effect of MEDI-563 on pulmonary function as assessed by changes from baseline in FEV_1
6) To describe the effect of MEDI-563 on functional performance, measured by 6 Minute Walk Test (6MWT)

7) To describe the PK and IM of MEDI-563 in COPD subjects

8) To assess the effect of MEDI-563 on dyspnea symptom as measured by the Modified Medical Research Council (MMRC) Dyspnea Scale

9) To assess the effect of MEDI-563 on symptom scores as measured by visual analogue scales (VAS). Symptom scores include cough, breathlessness, sputum purulence, and sputum production.

10) To assess the effect of MEDI-563 on the use of concomitant medications

11) To assess all-cause mortality in the 1 year post-randomization amongst all subjects randomized to treatment.

12) To evaluate the effect of MEDI-563 on blood and sputum biomarkers.

13) To assess the effect of MEDI-563 on healthcare resource utilization and economics.

14) To assess the effect of MEDI-563 on total serum immunoglobulin E (IgE) and IgE fluorescence enzyme immunoassay (FEIA) for common aeroallergens

15) To develop and test clinical prediction rules (diagnostic tools) for discriminating COPD phenotypes

3 Study Design

3.1 Overview of Study Design

This is a Phase 2a, randomized, double-blind, placebo-controlled, multicenter study evaluating the effect of multiple SC doses of MEDI-563 on the rate of moderate-to-severe AECOPD in adult subjects with moderate-to-severe COPD as defined by GOLD (GOLD, 2009). Eligible subjects will have a documented history of AECOPD within 2-12 months prior to Day 1 and a sputum eosinophil count of ≥ 3.0% within 12 months prior to, or at screening. The definition of AECOPD is given in Section 5.3.7.1.

Subjects will be screened between Day -56 and Day -29. Prior to randomization, all subjects will undergo a 28-day run-in period (Day -28 to Day -1), during which their current ICS and/or long-acting β-agonist combination product will be replaced with Symbicort® (budesonide/formoterol fumarate) 200/6 µg/inhalation: 2 inhalations twice daily if FEV_1 is < 50% predicted or Spiriva® (tiotropium bromide monohydrate) 18 µg/inhalation once daily if 50% ≤ FEV_1 < 80% predicted (see Section 4.5.5). The subjects will be provided with a short-acting β2-agonist for symptom relief during the study (terbutaline sulphate, Bricanyl®). Subjects who remain clinically stable during the 28-day run-in period and meet eligibility

criteria will continue the maintenance treatment with Symbicort® or Spiriva® and may be randomized into the study to receive investigational product as an add-on therapy for 48 weeks. Approximately 90 subjects from multiple sites will be randomized in a 1:1 ratio to receive either 100 mg SC MEDI-563 or placebo. Investigational product (MEDI-563 or placebo) will be administered subcutaneously in an outpatient setting every 28 days for the first 3 doses and then every 56 days for the next 5 doses up to Day 337 (total 8 doses). Subjects will be followed for a total of 32 weeks (to Day 561). Post Day 561, subjects will continue until peripheral blood eosinophil counts return to 50 cells/μL or 20% of baseline.

Baseline measurements at screening will include evaluation of disease activity; pulmonary function tests (forced vital capacity [FVC], FEV_1); patient-reported outcomes (SGRQ-C, CRQ-SAS, MMRC dyspnea scale, EXACT-PRO, patient symptom scores [VAS]); analysis of eosinophil-generated proteins; sputum induction for analysis to include cell count and biomarkers; parasite serology and stool sampling (if applicable); medical assessment, and pulse oximetry.

The following evaluations will be conducted during the course of the study as described in Table 5.2-1. Evaluations will include assessments of disease activity; pulmonary function testing; analysis of eosinophil and basophil activation proteins; inflammation markers associated with COPD and the acute phase response, cytokines, tryptase, in serum and sputum; assessment of exacerbations; use of concomitant medications; patient-reported outcomes (SGRQ-C, CRQ-SAS, MMRC dyspnea scale, VAS symptoms, EXACT-PRO); functional assessment (6MWT); COPD severity (BODE index); safety assessments (AE and SAE); physical examination, vital signs, oxygen saturation, serum chemistry, hematology, urinalysis, PK, and IM. Not all evaluations will be done at each visit. In the event of a moderate-to-severe exacerbation, additional evaluations will be done as described in Table 5.2-2.

A study flow diagram is presented in Figure 3.1-1.

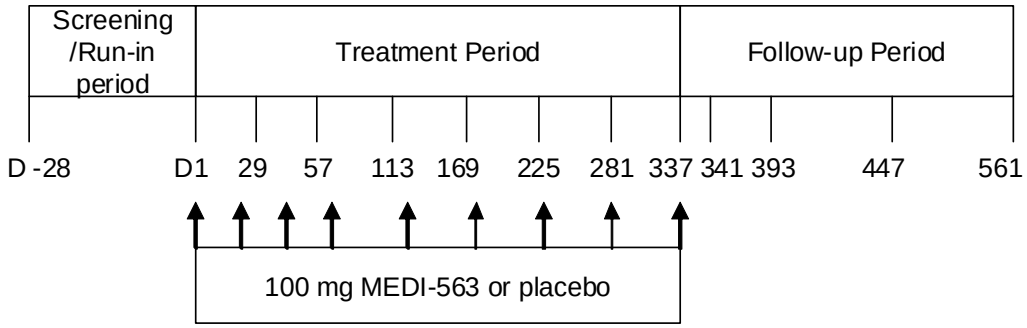

Figure 3.1-1 Study Flow Diagram

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

3.2 Estimated Duration of Subject Participation

Subject enrollment is anticipated to take approximately 12 months. Subjects will be in the study for approximately 88 weeks (up to 28 days for screening, 28 days run-in, 48 weeks [Day 1 to Day 337] of treatment, and 32 weeks of follow-up [to Day 561]).

3.3 Study-Stopping Criteria

If any of the following occur, administration of investigational product will be stopped and no additional subjects will be entered into the study:

1) Death in any subject in which the cause of death is assessed as related to investigational product
2) The occurrence of severe immune complex disease. (Severe immune complex disease is evoked by the deposition of antigen-antibody or antigen-antibody-complement complexes on cell surfaces, with subsequent involvement of breakdown products of complement, platelets, and polymorphonuclear leukocytes, and development of vasculitis; serum sickness and nephritis is common.)
3) Events that, in the opinion of the medical monitor and the Safety Monitoring Committee (SMC), contraindicate further dosing of additional subjects.

If any of the above-listed events occurs, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted (see Section 6.5) to determine whether dosing and study entry should be resumed, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the medical monitor and MedImmune SMC are required for resumption of the study in the event the

study is interrupted because of one of the above-listed events. Where applicable, regulatory authorities and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will be notified of any actions taken with the study.

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

Withdrawal criteria for individual subjects are provided in Section 4.2.3.

3.4 Rationale for Study Design, Doses, and Control Groups

The proposed study is a Phase 2a study to investigate the effect of multiple 100 mg SC doses of MEDI-563 on the rate of moderate-to-severe AECOPD in adult subjects with moderate-to-severe COPD who have a documented history of AECOPD within 2-12 months prior to Day 1 and a sputum eosinophil count of ≥ 3.0% in the previous 12 months or at screening. The double-blind, placebo-controlled, randomised clinical study is considered to be gold standard for the safety and efficacy assessment of a new therapy both by clinicians and drug regulatory authorities. Various ethical guidelines have been proposed to govern the performance of clinical trials and the appropriate application of placebo controlled studies.

Inclusion of adult subjects aged 40-85 years with moderate-to-severe COPD who have a documented history of AECOPD within 2-12 months prior to Day 1 and a sputum eosinophil count of ≥ 3.0% in the previous 12 months or at screening will provide data on the efficacy, safety and tolerability of MEDI-563 in a representative subject population. The number of subjects over 65 years with COPD is not insignificant and is still rising. These subjects may also benefit from new therapies for COPD.

3.4.1 Dose and Schedule Justification

Dose and schedule justifications for MEDI-563 in this study are based on results of early clinical studies (MI-CP158 and MI-CP197) in asthma patients. The dose of 100 mg corresponds to 0.625 mg/kg/month IV dose (assuming an average body mass of 80 kg and bioavailability of 50%). In MI-CP158, median peripheral blood eosinophil counts remained < 100 cells/µL up to Day 3 (median 50 cell/µL; range 0-70 cells/µL) in the lowest dose group (0.0003 mg/kg) and at least 84 days (median 0 cells/µL; range 0-220 cells/µL) in the highest dose groups (0.3-3.0 mg/kg).Following 3 monthly SC doses of MEDI-563 in MI-CP197, PK

modeling projects that lung tissue concentrations of MEDI-563 needed to deplete airway eosinophils is achieved in the 100 mg group during every 4-week and every 8-week dosing. The 20-mg dose achieves the projected levels with 4-week dosing but only about 50% of the time with every 8-week dosing. Finally, the 2-mg dose fails to achieve the target lung tissue concentrations of MEDI-563 with either every 4-week or every 8-week dosing. The expectation is that there will be significant ADCC eosinophil depletion in the airways at the 100-mg dose.

While higher lung tissue concentrations of MEDI-563 may be required for rapid airway eosinophil depletion expected during the every 4-week dosing period, once the majority of airway eosinophils are depleted, a 10-fold lower concentration of MEDI-563 is projected to be required to maintain eosinophil depletion in the blood. MI-CP197 PK simulations estimate that a dose of 100 mg given every 8 weeks will maintain peripheral blood eosinophil counts at zero.

Though MEDI-563 concentrations should be adequate in the lung tissue with the 100 mg dose, ADCC is also dependent upon expression of MEDI-563 target antigen (IL-5Rα) on eosinophils and the number of effector cells (primarily NK cells) in lung tissue. A reduction in IL-5Rα expression on eosinophils isolated from BAL fluid in asthmatics after allergen challenge has been demonstrated (Liu et al, 2002). Moreover, in vitro studies of eosinophils cultured with either IL-5 or granulocyte-macrophage colony-stimulating factor result in decreased surface expression of IL-5Rα (Liu et al, 2002a). With respect to effector cells, decreased proportions of NK cells have been observed in the sputum of asthmatic patients (Louis et al, 1997).

To compensate for the above potential negative effects on ADCC activity, MEDI-563 or placebo will be initially administered every 4 weeks for the first 3 doses and then every 8 weeks for the next 5 doses. It is expected that dosing every 4 weeks will double the mean MEDI-563 lung tissue concentration and will deplete the majority of airway tissue eosinophils relative to dosing every 8 weeks.

An 11-month treatment duration is considered sufficient to show an effect on the primary and secondary variables selected for this study and current nonclinical toxicology data supports this treatment duration.

4 Study Procedures

4.1 Subject Participation and Identification

Study participation begins once written informed consent is obtained (see Section 10.3 for details). Once informed consent is obtained, a subject identification number will be assigned by a central system (eg, an interactive voice/web response system; IXRS), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The subject identification number will be used to identify the subject during the screening process and throughout study participation, if applicable.

4.2 Subject Selection and Withdrawal

The subjects in this study will be adult subjects aged 40-85 years with moderate-to-severe COPD as defined by GOLD (GOLD, 2009) who have a documented history of AECOPD within 2-12 months prior to Day 1 and a sputum eosinophil count of ≥ 3.0% within 12 months prior to, or at screening.

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

4.2.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1) Subjects aged 40-85 years at the time of screening.
2) Written informed consent obtained from the subject prior to performing any protocol-related procedures.

3) Documented history of moderate to severe COPD with a post-bronchodilator $FEV_1/FVC < 0.70$ and a post-bronchodilator $FEV_1 < 80\%$ predicted at screening.

4) Documented history of 1 or more AECOPD that required treatment with systemic corticosteroids and/or antibiotics, or hospitalization within 8 weeks - 52 weeks prior to Day 1.

5) Eosinophilia ≥ 3.0% demonstrated on sputum within 12 months prior to, or at screening.

6) Clinically stable and free from an acute exacerbation of COPD for 8 weeks prior to Day 1.

7) Current smoker or ex-smoker with a tobacco history of ≥ 10 pack-years (1 pack year = 20 cigarettes smoked per day for 1 year).

8) Female subjects of childbearing potential who are sexually active with non-sterilized male partner must use adequate contraception from screening through the end of the study. An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are included, the recommended methods of contraception are described in Table 4.2.1-1. Sustained abstinence is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

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

Table 4.2.1-1 Recommended Methods of Contraception

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

10) Females not of childbearing potential must have been surgically sterilized (eg, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or postmenopausal (defined as at least 1 year since last regular menses) and follicle stimulating hormone (FSH) > 23 IU/L according to a central laboratory.

11) Sterilized males must be at least one year post vasectomy or must use adequate contraception (see Table 4.2.1-1) if less than one year post vasectomy.

12) Ability and willingness to complete follow-up period as required by the protocol.

13) Subjects receiving allergy immunotherapy must be on a stable dose for the preceding 90 days prior to Day 1.

14) Able to read and write.

4.2.2 Exclusion Criteria

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

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

2) Significant or unstable ischemic heart disease, arrhythmia, cardiomyopathy, heart failure, renal failure, uncontrolled hypertension as defined by the Investigator, or any other relevant cardiovascular disorder as judged by the Investigator.

3) Pregnant, breastfeeding, or lactating women.

4) Known history of allergy or reaction to any component of the investigational product formulation, budesonide/formoterol preparations, tiotropium bromide or terbutaline sulphate or any of their excipients.

5) History of anaphylaxis to any other biologic therapy.

6) Donation or transfusion of blood, plasma or platelets within the past 90 days prior to screening.

7) Other significant pulmonary disease as a primary diagnosis (eg, cystic fibrosis, bronchiecstasis, alpha-1 antitrypsin deficiency, interstitial lung disease; pulmonary hypertension other than cor pulmonale) if a subject is diagnosed with any other pulmonary disease as a secondary diagnosis, they may be included if, in the opinion of the investigator or medical monitor the inclusion does not compromise the interpretation of the study.

8) Receiving long-term oxygen therapy (LTOT) at entry into the study. Long-term oxygen therapy is defined as use of oxygen for a minimum of 15 hours per day.

9) Subjects who have a past or present disease or disorder, which as judged by the investigator and the medical monitor, may either put the subject at risk because of participation in the study, or may affect the outcome of this study. Subjects, who have epilepsy, must be on a stable dose of medication for 30 days prior to Day 1.

10) Influenza vaccination within 3 weeks before sputum collection at screening (Day -56).

11) Fever > 37.8°C (100°F) measured using the tympanic temperature (or equivalent oral/rectal/axillary temperature) at Day 1.

12) Use of immunosuppressive medication, including inhaled (other than Symbicort®), topical, ocular, nasal or rectal corticosteroids and systemic steroids within 28 days before randomization (Day 1) into the study.

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

14) Receipt of any novel investigational medicinal product within 3 months before the first dose of investigational product in this study and through the end of the study.

15) Seropositive for hepatitis B surface antigen, hepatitis C, or human immunodeficiency virus (HIV-1 or HIV-2).

16) Unexplained diarrhea within 30 days prior to screening; or a diagnosis of a helminth parasitic infestation within 6 months prior to screening; history of an untreated systemic helminth parasitic infection; history of living with a person known to have had a helminth parasitic infestation within 12 months prior to screening ; history of recent travel to areas where parasite infestations are endemic within 3 months before screening.

17) Any subjects that have positive serum serology during the screening/run-in period to *Strongyloides stercoralis* will be excluded. Subjects with a positive serology to *Schistosoma mansoni*, *Taenia solium*, or *Ascaris lumbricoides* will undergo a confirmatory stool sampling per local guidelines[1]. If the stool sampling is positive for *Schistosoma mansoni* or *Taenia solium* the subject will be excluded. All subjects with a positive serology for *Ascaris lumbricoides,* whether stool sampling is positive or negative, must be administered a single oral dose of 400mg albendazole. If albendazole is not licensed, the subject will be treated per local standard of care.

18) History of alcohol or drug abuse within the past year that required treatment that the investigator felt or medical monitor felt would compromise the study data interpretation.

19) Past or current malignancy within the past 5 years except adequately treated non-invasive basal cell and squamous cell carcinoma of the skin and cervical carcinoma-in-situ treated with apparent success more than 1 year prior to screening.

20) Subjects who in the opinion of the investigator or qualified designee have evidence of active tuberculosis (TB), either treated or untreated, or latent TB without completion of an appropriate course of treatment or appropriate ongoing

prophylactic treatment. Evaluation will be according to the local standard of care and may consist of history and physical examinations, chest x-ray, and/or TB test (eg, purified protein derivative[1] testing, etc with the standard of care as determined by local guidelines).

21) Scheduled in-patient hospitalization during the course of the study.

22) Subjects participating in, or scheduled for, an intensive COPD rehabilitation program (subjects who are in the maintenance phase of a rehabilitation program are eligible to take part).

23) Subjects with lung volume reduction surgery within the 12 months prior to screening.

24) Employees of the clinical study site or family members (first-degree relatives) of such individuals.

25) Current diagnosis of asthma according to Global Initiative for Asthma (GINA) guidelines (GINA, 2009).

26) Previous treatment with MEDI-563.

4.2.3 Withdrawal Criteria

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 or lost to follow-up

2) Adverse event that, in the opinion of the investigator, contraindicates further dosing.

3) Pregnancy

4) Severe noncompliance to protocol as judged by the investigator and/or sponsor

5) Incorrect enrolment ie, the subject does not to meet the required inclusion/exclusion criteria for the study

6) Anaphylactic reaction to MEDI-563 requiring epinephrine treatment (defined in

[1] Test procedures for TB and stool sampling for Schistosoma mansoni, Taenia solium, and Ascaris lumbricoides will be agreed and documented by country and approved by MedImmune prior to recruitment.

Appendix 1).

7) Development of Grade 3 or Grade 4 helminth parasitic infestation (see Section 6.2.1 for severity assessments).

Withdrawal of consent: If consent is withdrawn, the subject will not receive any further investigational product or further study observation. The investigator will make every attempt to follow the subject's peripheral blood eosinophil level until their peripheral blood eosinophil counts return to 50 cells/μL or 20% of the Day 1 value. Once a subject's peripheral blood eosinophil count returns to 50 cells/μL or 20% of the Day 1 value, the study site will be notified and the subject will no longer be followed. If a subject does not want to return, the investigator will advise the subject of the risks relating to a low peripheral blood eosinophil count.

Lost to follow-up: Subjects will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status on Day 561.

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

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

Subjects who are permanently discontinued from receiving investigational product will be asked to complete Day 337 (minus administration of investigation product) then will be followed for safety through the full study follow up period (through Day 561, including study day window), including the collection of any protocol-specified blood, urine, or sputum specimens, unless consent is withdrawn, lost to follow-up, or enrolled in another clinical study.

4.2.4 Replacement of Subjects

Subjects who withdraw or are withdrawn from the study will not be replaced.

4.2.4.1 Rescreening of Subjects

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

If a subject fails to meet all eligibility criteria but in the clinical judgment of the investigator, the assessments undertaken are not considered representative of the usual status of a subject's COPD or general health, then eligibility criteria may be re-assessed on one further occasion (rescreening).

If a subject originally screen failed as a result of testing positive for Hepatitis A according to exclusion #15, this subject will be allowed to be re-screened. In addition, if this subject fails to meet all eligibility criteria but in the clinical judgment of the investigator, the assessments undertaken are not considered representative of the usual status of a subject's COPD or general health, then eligibility criteria may be re-assessed on one further occasion (rescreening).

If a subject originally screen failed as a result of testing positive for *Schistosoma mansoni, Taenia solium, or Ascaris lumbricoides* according to exclusion #16, this subject will be allowed to be re-screened. In addition, if this subject fails to meet all eligibility criteria but in the clinical judgment of the investigator, the assessments undertaken are not considered representative of the usual status of a subject's COPD or general health, then eligibility criteria may be re-assessed on one further occasion (rescreening).

Subjects who fail to meet eligibility criteria due to an exacerbation prior to Day -28 may be rescreened after a minimum of 1 month wait. In this case, rescreening may occur up to two times prior to Day -28. Rescreened subjects must be given a new subject identification number and undergo all screening procedures, including informed consent.

If a subject has started the 28-day run-in period with Symbicort® or Spiriva® and has a mild, moderate or severe exacerbation, the subject may remain on Symbicort® or Spiriva® for 8 weeks following the end of the exacerbation before receiving their first dose of investigational product (MEDI-563 or placebo). The subject will only be dosed with investigational product if all the eligibility criteria are met as for Day 1. A subject may not receive Symbicort® or Spiriva® for longer than an 8-week period following the end of the exacerbation. In the 8-week period subjects will undergo assessments as for Day -28.

The medical monitor must approve the rescreening of any subject in advance of a rescreening visit. If a subject is rescreened, a separate subject identification number will be allocated by the IXRS. The time between the two screening visits is dependent upon the clinical judgment of the investigator. At the rescreening visit, the subject should repeat all screening period (Day-56) procedures, except as specified below. If ≤ 14 days has elapsed between the screening visits, the following tests do not need to be repeated unless clinically indicated: serum for HIV, Hep B surface antigen, Hep C antibody, parasite serology and stool sampling (if applicable), serum hematology, serum chemistry, urinalysis. For women of childbearing potential, serum pregnancy test should not be repeated if ≤ 7 days have elapsed between visits. The following assessments do not need to be repeated; sputum cell count (if eosinophilia ≥ 3.0% demonstrated on sputum within 12 months), sputum biomarkers, RNA profiling.

4.3 Treatment Assignment

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

Subjects will be randomized at a 1:1 ratio to receive either MEDI-563 or placebo.

The randomization procedure is as follows:

- The subject arrives at the clinic, outpatient office or hospital for the Day 1 visit.
- The investigator or designee confirms that written informed consent has been obtained, that the subject has successfully completed the 28-day run-in period and that the subject meets all eligibility criteria.
- The investigator or designee calls or logs onto the IXRS and provides the subject identification number and subject's baseline characteristics used to verify that it is the same subject.
- The IXRS assigns a treatment group and investigational product kit number(s) to the subject.
- A confirmatory fax with this information is sent to the Investigational Product Manager and the investigator/designee.

Investigational product (MEDI-563 or placebo) must be administered as soon as possible after receipt of the investigational product kit number(s). 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*.

4.4 Blinding

This is a double-blind study in which MEDI-563 and placebo are not indistinguishable in appearance. Neither the subject 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 (ICH E9). Since MEDI-563 and placebo are not indistinguishable in appearance, investigational product will be handled by an unblinded investigational product manager at the site. An independent investigational product monitor will be unblinded to perform investigational product accountability. Study site personnel can administer the medication once it is reconstituted.

All other study site personnel including the investigators, study nurses, and coordinators, as well as the subjects, will be blinded to treatment assignment. All MedImmune personnel or designees who are directly involved with the conduct of the study will also be blinded to treatment assignments. The vendor for packaging and labeling of the clinical supplies, IXRS personnel, the Investigational Product Manager, MedImmune Clinical Research Pharmacy Service (CRPS) personnel, and designated persons in MedImmune Quality Assurance are the only individuals who will have access to information that may identify a subject's treatment allocation. These individuals must not reveal randomization or treatment information to anyone or participate in or be associated with the evaluation of study subjects.

4.4.1 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. Prior to unblinding the investigational product allocation for an individual subject, the investigator must first attempt to contact the medical monitor to discuss the medical emergency and the reason for wanting to unblind. 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.

4.4.2 Unblinding for Primary Efficacy Analysis Purposes

The primary efficacy analysis is planned for this study as described in Section 7.4. The primary efficacy analysis methodology and the review of the resulting data by the Sponsor will be described in the Statistical Analysis Plan (SAP). The actual data from the primary efficacy analysis will not be communicated to personnel at the investigational sites or to enrolled subjects. The actual data from the primary efficacy analysis will only be communicated to limited personnel at MedImmune, which will be specified in a separate unblinding plan. No member of the study team will be unblinded. Details of the unblinding process will be documented in a separate unblinding plan.

4.4.3 Unblinding Due to the Known Effects of MEDI-563

Eosinophil and basophil counts in peripheral blood can be a source of unblinding due to the known effects of MEDI-563. Thus, once subjects are treated, eosinophil counts (including ECP, eosinophil derived neurotoxin [EDN], major basic protein [MBP], IL-5, and eotaxin) basophil counts and WBC differential (absolute and %) counts will not be communicated to the site personnel who evaluate the subjects clinically, except if the information is required for management of AEs. If unblinding needs to occur due to an AE, communication between the site and the MedImmune medical monitor should happen prior to disclosure of the eosinophil counts to the site. During an exacerbation, laboratory analyses will be performed locally and these results will be reviewed by an unblinded physician /nursing /hospital staff member that is not involved with the study. If results are reviewed by the study physician, the differential WBC counts will be blinded.

When a subject completes the Day 561 visit, the central laboratory will review their Day 561 peripheral blood eosinophil counts and notify the study site whether the subject should continue in the study. Subjects who have a peripheral blood eosinophil count below 50 cells/µL or <20% of the value on Day 1 will return to the study site every 84 days for a blood draw (4 mL) until their peripheral blood eosinophil counts return to 50 cells/µL or ≥20% of the Day 1 value, whichever occurs first. Once a subject's peripheral blood eosinophil count returns to 50 cells/µL or ≥20% of the Day 1 value, the study site will be notified and the subject will no longer be followed.

4.5 Study Treatment

4.5.1 Investigational Product Supplies and Accountability

Investigational product will be supplied to the site in coded kits. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Detailed instructions are provided in the Investigational Product Manual.

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

MEDI-563: MEDI-563 is supplied as a [redacted] in a 3-cc single use glass vial, which should be reconstituted with [redacted] sterile water for injection. The reconstituted product will contain MEDI-563 at [redacted] with the following additional components: [redacted]

Placebo: Placebo is supplied as a sterile liquid containing [redacted] solution in a 3-cc single -use glass vial. The solution also contains [redacted]

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

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

4.5.2 Treatment Regimens

A total of 90 subjects will be randomized in a 1:1 ratio to receive either 100 mg SC of MEDI-563 or placebo. Investigational product (MEDI-563 or placebo) will be administered as a SC injection in the outpatient setting every 28 days for the first 3 doses and then every 56 days for the next 5 doses for a total of 8 doses to Day 337.

Table 4.5.2-1 Summary of Treatment Regimens

Dose Cohort	Number of Subjects	Treatment Regimen
1	45	100 mg MEDI-563 administered SC (50 mg in each arm) every 28 days for the first 3 doses and then every 56 days for the next 5 doses (Day 1, 29, 57, 113, 169, 225, 281 and 337).
	45	Placebo administered SC (one injection in each arm) every 28 days for the first 3 doses and then every 56 days for the next 5 doses (Day 1, 29, 57, 113, 169, 225, 281 and 337).

In addition, all subjects will receive Symbicort® 200/6 µg/inhalation: 2 inhalations twice daily if FEV_1 is < 50% predicted or Spiriva® 18 µg/inhalation once daily if $50\% \leq FEV_1 < 80\%$ predicted as maintenance therapy starting on Day -28. Subjects will receive Bricanyl® as rescue medication. The start of maintenance therapy will be based on spirometry measurements taken at Day -56. The following study drugs will be provided by MedImmune to the subjects throughout the study:

Trade Name: Symbicort® (see Appendix 2)

- Active ingredients: budesonide/formoterol fumarate dihydrate
- Excipients: lactose monohydrate

Trade Name: Spiriva® given via HandiHaler® (see

Appendix 3)

- Active ingredients: tiotropium bromide
- Excipients: lactose monohydrate

Trade Name: Bricanyl® Turbuhaler® (see

Appendix 4)

- Active ingredients: terbutaline sulphate
- Excipients: none

4.5.3 Investigational Product Preparation

The dose of investigational product for administration must be prepared by the designated investigational product manager at the site using aseptic technique. Detailed instructions regarding investigational product preparation can be found in the Investigational Product Manual that will be provided to the designated investigational product manager at the site.

Instructions for the reconstitution of lyophilized product for administration are as follows:

- To reconstitute, remove the plastic portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.
- The vials contain an overfill to allow the withdrawal of [redacted] of MEDI-563 when reconstituted following the directions described below.
  - SLOWLY add [redacted] of sterile water for injection to the vial. The vial should be tilted slightly and gently rotated or swirled for 60 seconds or until dissolution is complete. DO NOT SHAKE or VIGOROUSLY AGITATE the VIAL. This is a critical step to avoid prolonged foaming.
  - Reconstituted MEDI-563 should stand undisturbed at room temperature for a minimum of 2 minutes until the solution clarifies.
  - Reconstituted MEDI-563 should be inspected visually for particulate matter or discoloration prior to administration. The reconstituted solution should appear clear or slightly opalescent (a thin layer of micro-bubbles on the surface is normal and will not affect dosage). DO NOT use if there is particulate matter or if the solution is discolored.

Reconstituted MEDI-563 does not contain a preservative and should be administered promptly (within 6 hours) after reconstitution. MEDI-563 is supplied in single-use vials. DO NOT re-enter the vial.

4.5.4 Investigational Product Administration

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

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

The investigational product will be administered by SC injection, one injection in each arm. The investigator or qualified designee will inject the investigational product. The SC injections will be administered into the SC tissue of the triceps muscle of the arm. One injection should be administered in each arm.

The investigational product will be administered via a 26-gauge 3/8-inch needle. The person administering the dose will wipe the skin surface with alcohol and allow to air dry. The skin over the triceps muscle (excluding the muscle) will be pinched to isolate the SC tissue from the muscle. The needle will be inserted at a 90-degree angle approximately halfway into the SC tissues overlaying the triceps muscle. The 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 rubbed or massaged after injection.

4.5.4.1 Monitoring of Dose Administration

Vital signs (blood pressure, temperature, pulse rate, and respiration rate) will be obtained before investigational product administration on all treatment days. In addition, subjects will be monitored after investigational product administration for immediate drug reactions for a minimum of 2 hours with vital signs taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable, whichever is later.

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

Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death. See

Appendix 1 for the clinical criteria for defining anaphylaxis.

If an anaphylactic reaction occurs, the subject will be stabilized and once stabilized, a blood sample will be drawn from the subject as well as 1-2 hours after the event for analysis of serum tryptase).

4.5.5 Concomitant Medications

4.5.5.1 Restricted Concomitant Medication During the Study

Use of concomitant medications including over-the-counter medications, herbal supplements, vitamins, etc or any other medications that may interfere with the study results is not permitted from screening through Day 393. However, subjects may receive medications as supportive care or to treat AEs as deemed necessary by the investigator or the subject's physician.

Subjects will be asked to refrain from taking Symbicort® and Spiriva® for at least 12 hours prior to the next day's clinic visit and reliever medication (Bricanyl®) or any other medication used for COPD symptoms at least 6 hours prior to clinic visits, if possible. Subjects should not take Symbicort®, Spiriva®, Bricanyl® or any other medication used for COPD symptoms at home on the morning of clinic visits. The medications will be taken in clinic after completing the predose assessments

The following medications are considered exclusionary if given within 28 days prior to treatment assignment and are not permitted from Day -28 through Day 561 during the study.

The sponsor must be notified if a subject receives any of these during the study.

- Inhaled short-acting β2-agonists (Bricanyl or SABA given for spirometry measurements are exempt; reliever medication provided continues during study but is withheld 6 hours prior to each visit if possible)
- Oral β2-agonists as follows:
  - Short-acting formulations
  - Depot formulations
  - Long-acting formulations
  - Transdermal β2-agonists

- Parenteral β2-agonists
- Inhaled ephedrine/pseudo-ephedrine or chronic use of any medication containing oral ephedrine/pseudo-ephedrine (chronic use defined as more than 14 days).
- Inhaled glucocorticosteroids (except Symbicort® 200/6 µg/inhalation, which will be provided)
- Oral, parenteral and rectal glucocorticosteroids (except for the treatment of exacerbation)
- Depot parenteral glucocorticosteroids

4.5.5.2 Maintenance Therapy

The start of maintenance therapy will be based on spirometry measurements taken at Day -56. Subjects who receive an ICS and/or long-acting β-agonist combination product, will have this replaced with Symbicort® 200/6 µg/inhalation: 2 inhalations twice daily if FEV_1 is < 50% predicted or Spiriva® 18 µg/inhalation once daily if 50% ≤ FEV_1 < 80% predicted as maintenance therapy. For subjects with a FEV_1 < 50% predicted, Spiriva® may be added at the investigator's discretion. Bricanyl® 0.5 mg/dose will be used as reliever medication throughout the study. Subjects with FEV_1 < 50% predicted, who are taking Spiriva®, may continue to take Spiriva® but must also take Symbicort® for the duration of the study. If a subject's FEV_1 drops < 50% predicted, the subject will commence Symbicort® 200/6 µg/inhalation: 2 inhalations twice daily as per protocol. During the study and follow-up periods (excluding run-in period), changes in other COPD medication are permitted (eg, for the treatment of exacerbations).

Refer to Sections 4.5.5.3 and 4.5.5.4 for a list of concomitant COPD medication that are allowed during the study.

4.5.5.3 Concomitant Medication for Exacerbation Therapy

Every attempt must be made to treat subject with Symbicort®, Spiriva® or Bricanyl® if indicated in an exacerbation, however in the event that these medications are not available a different inhaled steroid or bronchodilator may be used.

Specific medications are allowed for the treatment of exacerbation after Day -28 and throughout the study:

- Oral steroids (ie, prednisolone 30 mg/day or methylprednisolone 24 mg/day for 14 days or as according to local clinical guidelines)
- Antibiotic treatment is allowed when signs of infection are present for 10 days or as according to local clinical guidelines
- Parenteral steroids (not depot formulations)

4.5.5.4 Allowed Concomitant Medication During the Study

The following medications are permitted for the relief of COPD symptoms if necessary:

- Inhaled short-acting anticholinergics unless subject is taking Spiriva® (ie, if $50\% \leq FEV_1 < 80\%$ predicted), then these are not allowed
- Inhaled long-acting anticholinergics unless subject is taking Spiriva® (ie, $50\% \leq FEV_1 < 80\%$ predicted), then these are not allowed
- Inhaled long acting β2-agoinists unless subject is taking Symbicort® (ie, if FEV_1 is < 50% predicted), then these are not allowed
- Xanthine-containing derivatives (If a subject is taking theophylline, the tablet strength must be noted in the eCRF and theophylline levels measured as per Table 5.2-1)
- Leukotriene antagonists and 5-lipoxygenase (5-LO) inhibitors
- Mucolytic agents
- Short courses (≤ 14 days) of medication containing oral ephedrine/pseudo-ephedrine are allowed but must be withheld 48 hours prior to a spirometry assessment (See Section 5.3.7.2.1)

4.5.6 Treatment Compliance

The administration of all medication (including investigational products) must be recorded in the appropriate sections of the electronic Case Report Form (eCRF) and the drug accountability/dispensing record. Symbicort® and Spiriva® inhalations will be recorded on a daily basis in the electronic Diary (eDiary) for morning and evening dose as “yes” or “no”. This does not mean that the subjects have an option not to take the study medication but will be used as a measure of compliance. Bricanyl® reliever medication use and number of inhalations will be recorded in the eDiary on a daily basis. Investigational product is administered by study site personnel, who will monitor compliance.

4.6 Subject Completion

An individual subject will be considered to have completed the study if the subject was followed up through the end of the study, defined as Day 561, 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 4.2.3).

4.7 End of the Study

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

5 Assessment of Efficacy and Clinical Pharmacology

5.1 Efficacy and Clinical Pharmacology Parameters

5.1.1 Efficacy Parameters

- Number of moderate-to-severe AECOPD experienced from Day 1 to Day 393
- Reduction in hospitalizations due to AECOPD
- Time to first moderate-to-severe AECOPD
- Health related quality of life measurements (HRQOL), SGRQ-C and CRQ-SAS
- Symptom scores, measured using MMRC Dyspnea Scale and VAS scales
- Pulmonary function
- BODE index
- Functional performance measured by the 6MWT

5.1.2 Clinical Pharmacology Parameters

- MEDI-563 concentration

- Anti- MEDI-563 antibodies
- Blood biomarkers
- Sputum biomarkers
- Sputum cell count
- Ribonucleic acid (RNA) transcript profiles

5.2 Schedule of Study Procedures

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

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

A schedule of study procedures is presented in Table 5.2-1, followed by a description of each visit. In addition, Table 5.2-2 describes the evaluations to be performed in the event of an exacerbation. A description of the study procedures is included in Section 5.2.5.

Table 5.2-1 Schedule of Study Procedures

Procedure	Screening Day -56 to Day -29/Run-in Day -28 to Day -1		Treatment Period								Follow up Period			
	Day -56	Day -28	Day 1	Day 29	Day 57	Day 113	Day 169	Day 225	Day 281	Day 337	Day 341	Day 393	Day 477	Day 561
Written informed consent/ Assignment of subject identification number	X													
Verify eligibility criteria	X		X											
Medical/Surgical history	X													
Smoking history status	X													
Safety														
Physical examination	X		X		X	X	X	X	X	X		X	X	X
Height (Day -56 only) and weight	X		X			X						X		
TB test (if applicable)	X													
Chest x-ray or CT scan (if not preformed in the last 12 months)	X													
12 lead ECG	X		X	X	X	X	X	X	X	X		X	X	X
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X		X	X	X	X	X	X	X	X		X	X	X
Hematology CBC at screening Day -56 analyzed at local and central lab	X		X	X	X	X	X	X	X	X		X	X	X
Parasite serology and stool sampling (if applicable)	X													

Table 5.2-1 Schedule of Study Procedures

Procedure	Screening Day -56 to Day -29/Run-in Day -28 to Day -1		Treatment Period								Follow up Period			
	Day -56	Day -28	Day 1	Day 29	Day 57	Day 113	Day 169	Day 225	Day 281	Day 337	Day 341	Day 393	Day 477	Day 561
Urinalysis	X		X	X	X	X	X	X	X	X		X	X	X
Pregnancy test (serum at screening and urine at all other visits)	X		X	X	X	X	X	X	X	X		X	X	X
HIV-1 antibody	X													
Hep B surface antigen, Hep C antibody	X													
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pneumococcal and annual influenza vaccination, if applicable (Section 5.3)	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Theophylline level (if applicable)			X			X		X		X			X	X
Patient Reported Outcomes (To be done before any clinical assessments)														
SGRQ-C	X		X	X	X	X	X	X	X	X		X	X	X
CRQ-SAS (First Administration form done at Day -56 with Follow-Up Administration form done at all other visits)	X		X	X	X	X	X	X	X	X		X	X	X
MMRC Dyspnea Scale	X		X	X	X	X	X	X	X	X		X	X	X

Table 5.2-1 Schedule of Study Procedures

Procedure	Screening Day -56 to Day -29/Run-in Day -28 to Day -1		Treatment Period								Follow up Period			
	Day -56	**Day -28**	**Day 1**	**Day 29**	**Day 57**	**Day 113**	**Day 169**	**Day 225**	**Day 281**	**Day 337**	**Day 341**	**Day 393**	**Day 477**	**Day 561**
VAS Symptom Scores	X		X	X	X	X	X	X	X	X		X	X	X
Patient-Reported Outcomes Questionnaire Study Coordinator form (PRO-Q)	X		X	X	X	X	X	X	X	X		X	X	X
Disease Activity														
eDiary (includes EXACT-PRO and daily and weekly medication assessment)		X	X	X	X	X	X	X	X	X	X	X	X	X
6 Minute Walk Test			X			X						X		
Assessment of AECOPD (includes CGI exacerbation severity & Anthonisen symptom score)	X		X	X	X	X	X	X	X	X	X	X	X	X
Health resource utilization assessment	X		X	X	X	X	X	X	X	X		X	X	X
Pulmonary Functions Tests														
Lung volumes			X									X		
Office spirometry pre- & post-bronchodilator	X		X	X	X	X	X	X	X	X		X	X	X
Supplemental O_2 status	X		X	X	X	X	X	X	X	X		X	X	X
Oxygen saturation (SpO_2)	X		X	X	X	X	X	X	X	X		X	X	X

Table 5.2-1 Schedule of Study Procedures

Procedure	Screening Day -56 to Day -29/Run-in Day -28 to Day -1		Treatment Period								Follow up Period			
	Day -56	**Day -28**	**Day 1**	**Day 29**	**Day 57**	**Day 113**	**Day 169**	**Day 225**	**Day 281**	**Day 337**	**Day 341**	**Day 393**	**Day 477**	**Day 561**
FeNO (optional)			X			X		X				X		
DLCO			X									X		
Pharmacokinetic/Immunogenicity Evaluation														
MEDI-563 Serum concentration			X	X	X	X	X	X	X	X	X	X	X	X
Anti-MEDI-563 Antibodies			X		X	X		X		X		X	X	X
Correlative Studies														
Safety Biomarkers			X											
Serum for total IgE & IgE FEIA			X					X						X
Serum/Plasma Biomarkers			X		X			X					X	X
Sputum Biomarkers	X		X		X			X						X
Sputum cell count (slide preparation)	X		X		X			X						X
RNA Transcript Profiling (PAXgene whole blood RNA)	X		X		X			X						X
Randomization			X											
Provide Symbicort® or Spiriva® for daily administration and Bricanyl® for rescue medication		X	X	X	X	X	X	X	X	X		X	X	
Investigational product			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**				

Table 5.2-1 Schedule of Study Procedures

Procedure	Screening Day -56 to Day -29/Run-in Day -28 to Day -1		Treatment Period								Follow up Period			
	Day -56	Day -28	Day 1	Day 29	Day 57	Day 113	Day 169	Day 225	Day 281	Day 337	Day 341	Day 393	Day 477	Day 561
administration														

AE = adverse event; AECOPD = acute exacerbations of COPD; CGI = Clinicians Global Impression; CPK = creatinine phosphokinase; CRP = C-reactive protein; CRQ-SAS = Chronic Respiratory Questionnaire self-administered standardized format; CT = computed tomography; DLCO = diffusion capacity of carbon monoxide; ECG = electrocardiogram; EXACT-PRO = EXAcerbations of Chronic pulmonary disease Tool - Patient Reported Outcome; FEIA = fluorescence enzyme immunoassay; FeNO= fractional exhaled nitric oxide; FEV_1=forced expiratory volume in 1 second; Hep = hepatitis; HIV = human immunodeficiency virus; IgE = immunoglobulin-E; IM = immunogenicity; MMRC = Modified Medical Research Council; PK = pharmacokinetics; RNA = ribonucleic acid; SAE =serious adverse event; SGRQ-C = COPD-Specific Saint George's Respiratory Questionnaire; TB = tuberculosis; VAS = visual analogue scale

Table 5.2-2 Schedule of Subject Evaluations in the Event of a Moderate-to-Severe Exacerbation

Procedure	At the Time of Exacerbation	14 ± 3 days Postexacerbation
Exacerbation symptom assessment based on Anthonisen definition	X	
Vital signs	X	X
12-lead ECG	X	X
Assessment of AEs/SAEs	X	X
Physical examination	X	X
Concomitant medications	X	X
Chest x-ray or CT scan (if indicated)	X	
Spirometry	X	X
VAS Symptom Scores	X	X
Hematology and serum Chemistry (local labs)	X	X
Serum for biomarker analysis	X	X
Plasma for biomarker analysis	X	X
Sputum for biomarker analysis	X	X
Sputum for cell count (slide preparation)	X	X
Spontaneous sputum for bacterial cultures (local labs)	X	
Spontaneous sputum for viral RT-PCR	X	
RNA Transcript Profiling (PAXgene whole blood RNA)	X	
AECOPD Inpatient form (for exacerbation resulting in hospitalization only)		X
CRQ-SAS	X	X
CGI exacerbation severity	X	X
PRO-Q	X	X

AE = adverse event; AECOPD = acute exacerbation in COPD; CGI = Clinician Global Impression; CRP = C-reactive protein; CRQ-SAS = Chronic Respiratory Questionnaire self-administered standardized format; CT = computed tomography; ECG = electrocardiogram; RNA = ribonucleic acid; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; VAS = visual analogue scale.

Every attempt will be made to collect the assessments described in Table 5.2-2 in the event of a moderate-to-severe exacerbation. Hematology, biochemistry and bacterial culture assessments will be analyzed by the local laboratory and the hematology results will be

reviewed by an independent physician/ hospital staff member. If the study physician reviews the laboratory results, the eosinophil counts, basophil counts, and WBC counts must be blinded. Beta agonists will not be withheld prior to spirometry in the event of an exacerbation.

5.2.1 Screening

All screening procedures must be performed from Day -56 to Day -29, unless otherwise specified. The screening evaluations may be carried out over more than one visit. Written informed consent and any locally required authorization (eg, HIPAA in the US, EU Data Privacy Directive authorization in the EU must be obtained prior to performing any protocol-specific procedures, including screening evaluations. However, if evaluations that have been performed for other purposes prior to informed consent are otherwise suitable for use as screening evaluations, those evaluations need not be repeated if the subject consents to allow use.

5.2.1.1 Screening: Days -56 to -29

1) Obtain written informed consent and appropriate privacy act document authorization
2) Assign a subject identification number
3) Verify eligibility criteria
4) Patient-reported outcomes assessments
   a) SGRQ-C
   b) CRQ-SAS
      (First Administration form done at Day -56 with Follow-Up Administration form done at all other visits)
   c) MMRC Dyspnea Scale
   d) VAS symptom scores
5) PRO-Q
6) Perform medical/surgical history and smoking history status
7) Perform physical examination
8) Measure height and weight (height to be collected at Day -56 only)
9) Perform TB test, if applicable

10) Perform a chest x-ray or computed tomography (CT)-scan (if one has not been performed in the previous 12 months)
11) Perform 12-lead electrocardiogram (ECG; 3 separate ECG recordings required)
12) Perform disease activity assessments
    a) Assessment of AECOPD (including Clinicians Global Impression [CGI] exacerbation severity and assessment based on Anthonisen exacerbation definition)
    b) Collect health resource utilization data
13) Perform pulmonary function tests
    a) Spirometry pre- and post-bronchodilator
    b) Supplemental oxygen (O_2) status
    c) Measure oxygen saturation (SpO_2)
14) Collect blood for screening samples (subjects must be fasting for at least 8 hours):
    a) Whole blood PAXgene for RNA
    b) Hematology

    Hematology to be collected for central lab and local lab (Day -56 only) analysis
    c) Serum chemistry
    d) Parasite serology and stool sampling (if applicable)
    e) Serum pregnancy test
    f) Hepatitis B surface antigen, hepatitis C antibody
    g) HIV-1 antibody
15) Collect sputum for biomarker analysis and cell count
16) Collect urine for urinalysis
17) Assess vital signs
18) Assess for AEs and SAEs
19) Pneumococcal vaccination and an annual influenza vaccination will be administered unless the subject has received it prior to study start. If a subject has an egg intolerance, the vaccination may be omitted
20) Record concomitant medications

5.2.1.2 Run-in: Day -28 ± 3 days

1) Assess for AEs and SAEs
2) Record concomitant medications

3) Provide Symbicort® or Spiriva® product for daily administration, Bricanyl® as reliever (rescue) medication, and instructions for use

4) Prior to subject's departure, provide the subject with the eDiary device with instructions of usage and completion of EXACT-PRO and symptom diary daily in the evening

5.2.2 Treatment Period

5.2.2.1 Day 1 ± 3 days: First Injection

1) Verify eligibility criteria

2) Patient reported outcomes assessments
   a) SGRQ-C
   b) CRQ-SAS
   c) MMRC Dyspnea Scale
   d) VAS symptom scores

3) PRO-Q

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

5) Measure weight

6) Perform 12-lead ECG (3 separate ECG recordings required)

7) Perform disease activity assessments
   a) Review the daily and weekly medication assessment as recorded in the subject's eDiary
   b) Perform 6 Minute Walk Test
   c) Assessment of AECOPD
   d) Collect health resource utilization data

8) Perform pulmonary function tests
   a) Lung volumes
   b) Spirometry pre- and post-bronchodilator
   c) Supplemental O_2 status
   d) Measure SpO_2
   e) fractional exhaled nitric oxide (FeNO; optional)
   f) Diffusion capacity for carbon monoxide (DLCO)

9) Collect predose blood for:
   a) Serum chemistry
   b) Hematology
   c) MEDI-563 serum concentration
   d) Anti-MEDI-563 antibodies
   e) Safety biomarkers
   f) Serum for total IgE and IgE FEIA
   g) Biomarker analysis
   h) Whole blood PAXgene for RNA
   i) Theophylline level (if applicable)
10) Collect sputum for biomarker analysis and cell count
11) Collect urine for urinalysis and urine pregnancy test; ensure result is negative
12) Assess for AEs and SAEs
13) Record concomitant medications
14) Randomize and assign study product kit number
15) Take vital signs as described in Section 5.3.1.3
16) Administer investigational product
17) Provide Symbicort® or Spiriva® product for daily administration, Bricanyl® as reliever (rescue) medication, and instructions for use

5.2.2.2 Day 29 ± 3 days: Second Injection/Follow-up after First Injection

1) Patient-reported outcomes assessments
   a) SGRQ-C
   b) CRQ-SAS
   c) MMRC Dyspnea Scale
   d) VAS symptom scores
2) PRO-Q
3) Perform 12-lead ECG (1 ECG recording required)
4) Perform disease activity assessments
   a) Review the daily and weekly medication assessment as recorded in the subject's eDiary
   b) Assessment of AECOPD

c) Collect health resource utilization data

5) Perform pulmonary function tests
   a) Spirometry pre- and post-bronchodilator
   b) Supplemental O_2 status
   c) Measure SpO_2
6) Collect predose blood for:
   a) Serum chemistry
   b) Hematology
   c) MEDI-563 serum concentration
7) Collect for urine for urinalysis and a urine pregnancy test; ensure pregnancy test result is negative
8) Assessment of AEs and SAEs
9) Record concomitant medications
10) Take vital signs as described in Section 5.3.1.3
11) Administer investigational product
12) Provide Symbicort® or Spiriva® product for daily administration, Bricanyl® as reliever (rescue) medication, and instructions for use

5.2.2.3 Day 57 ± 3 days: Third Injection/Follow-up after Second Injection

1) Patient-reported outcomes assessments
   a) SGRQ-C
   b) CRQ-SAS
   c) MMRC Dyspnea Scale
   d) VAS symptom scores
2) PRO-Q
3) Perform physical examination
4) Perform 12-lead ECG (one ECG recording required)
5) Perform disease activity assessments
   a) Review the daily and weekly medication assessment as recorded in the subject's eDiary
   b) Assessment of AECOPD
   c) Collect health resource utilization data

6) Perform pulmonary function tests
   a) Spirometry pre- and post-bronchodilator
   b) Supplemental O_2 status
   c) Measure SpO_2
7) Collect predose blood for:
   a) Serum chemistry
   b) Hematology
   c) MEDI-563 serum concentration
   d) Biomarker analysis
   e) Whole blood PAXgene for RNA
   f) Anti-MEDI563 antibodies
8) Collect sputum for biomarker analysis and cell count
9) Collect for urine for urinalysis and a urine pregnancy test; ensure pregnancy test result is negative
10) Assessment of AEs and SAEs
11) Record concomitant medications
12) Take vital signs as described in Section 5.3.1.3
13) Administer investigational product
14) Provide Symbicort® or Spiriva® product for daily administration, Bricanyl® as reliever (rescue) medication, and instructions for use

5.2.2.4 Day 113 ± 7 days: Fourth Injection/Follow-up after Third Injection

1) Patient-reported outcomes assessments
   a) SGRQ-C
   b) CRQ-SAS
   c) MMRC Dyspnea Scale
   d) VAS symptom scores
2) PRO-Q
3) Perform physical examination
4) Measure weight
5) Perform 12-lead ECG (one ECG recording required)
6) Perform disease activity assessments

a) Review the daily and weekly medication assessment as recorded in the subject's eDiary

b) Perform 6 Minute Walk Test

c) Assessment of AECOPD

d) Collect health resource utilization data

7) Perform pulmonary function tests

a) Spirometry pre- and post-bronchodilator

b) Supplemental O_2 status

c) Measure SpO_2

d) FeNO (optional)

8) Collect predose blood for:

a) Serum chemistry

b) Hematology

c) MEDI-563 serum concentration

d) Anti-MEDI-563 antibodies

e) Theophylline level (if applicable)

9) Collect for urine for urinalysis and a urine pregnancy test; ensure pregnancy test result is negative

10) Assessment of AEs and SAEs

11) Record concomitant medications

12) Take vital signs as described in Section 5.3.1.3

13) Administer investigational product

14) Provide Symbicort® or Spiriva® product for daily administration, Bricanyl® as reliever (rescue) medication, and instructions for use

5.2.2.5 Day 169 ± 7 days: Fifth Injection/Follow-up after Fourth Injection

1) Patient-reported outcomes assessments

a) SGRQ-C

b) CRQ-SAS

c) MMRC Dyspnea Scale

d) VAS symptom scores

2) PRO-Q

3) Perform physical examination
4) Perform 12-lead ECG (one ECG recording required)
5) Perform disease activity assessments
   a) Review the daily and weekly medication assessment as recorded in the subject's eDiary
   b) Assessment of AECOPD
   c) Collect health resource utilization data
6) Perform pulmonary function tests
   a) Spirometry pre- and post-bronchodilator
   b) Supplemental O_2 status
   c) Measure SpO_2
7) Collect blood for:
   a) Serum chemistry
   b) Hematology
   c) MEDI-563 serum concentration
8) Collect for urine for urinalysis and a urine pregnancy test; ensure pregnancy test result is negative
9) Assessment of AEs and SAEs
10) Record concomitant medications
11) Take vital signs as described in Section 5.3.1.3
12) Administer investigational product
13) Provide Symbicort® or Spiriva® product for daily administration, Bricanyl® as reliever (rescue) medication, and instructions for use

5.2.2.6 Day 225 ± 7 days: Sixth Injection/Follow-up after Fifth Injection

1) Patient-reported outcomes assessments
   a) SGRQ-C
   b) CRQ-SAS
   c) MMRC Dyspnea Scale
   d) VAS symptom scores
2) PRO-Q
3) Perform physical examination

4) Perform 12-lead ECG (one ECG recording required)

5) Perform disease activity assessments

   a) Review the daily and weekly medication assessment as recorded in the subject's eDiary

   b) Assessment of AECOPD

   c) Collect health resource utilization data

6) Perform pulmonary function tests

   a) Spirometry pre- and post-bronchodilator

   b) Supplemental O_2 status

   c) Measure SpO_2

   d) FeNO (optional)

7) Collect predose blood for:

   a) Serum chemistry

   b) Hematology

   c) MEDI-563 serum concentration

   d) Anti-MEDI-563 antibodies

   e) Serum for total IgE and IgE FEIA

   f) Biomarker analysis

   g) Whole blood PAXgene for RNA

   h) Theophylline level (if applicable)

8) Collect sputum for biomarker analysis and cell count

9) Collect for urine for urinalysis and a urine pregnancy test; ensure pregnancy test result is negative

10) Assessment of AEs and SAEs

11) Record concomitant medications

12) Take vital signs as described in Section 5.3.1.3

13) Administer investigational product

14) Provide Symbicort® or Spiriva® product for daily administration, Bricanyl® as reliever (rescue) medication, and instructions for use

5.2.2.7 Day 281 ± 7 days: Seventh Injection/Follow-up after Sixth Injection

Same as Day 169 see Section 5.2.2.5.

5.2.2.8 Day 337 ± 7 days: Eighth Injection/Follow-up after Seventh Injection

1) Patient-reported outcomes assessments
   a) SGRQ-C
   b) CRQ-SAS
   c) MMRC Dyspnea Scale
   d) VAS symptom scores
2) PRO-Q
3) Perform physical examination
4) Perform 12-lead ECG (one ECG recording required)
5) Perform disease activity assessments
   a) Review the daily and weekly medication assessment as recorded in the subject's eDiary
   b) Assessment of AECOPD
   c) Collect health resource utilization data
6) Perform pulmonary function tests
   a) Spirometry pre- and post-bronchodilator
   b) Supplemental O_2 status
   c) Measure SpO_2
7) Collect predose blood for:
   a) Serum chemistry
   b) Hematology
   c) MEDI-563 serum concentration
   d) Anti-MEDI-563 antibodies
   e) Theophylline level (if applicable)
8) Collect for urine for urinalysis and a urine pregnancy test; ensure pregnancy test result is negative
9) Assessment of AEs and SAEs
10) Record concomitant medications
11) Take vital signs as described in Section 5.3.1.3
12) Administer investigational product

13) Provide Symbicort® or Spiriva® product for daily administration, Bricanyl® as reliever (rescue) medication, and instructions for use

5.2.3 Follow-up Period

5.2.3.1 Day 341 ± 3 days

1) Perform disease activity assessments
   a) Review the daily and weekly medication assessment as recorded in the subject's eDiary
   b) Assessment of AECOPD
2) Collect blood for:
   a) MEDI-563 serum concentration
3) Take vital signs
4) Assess for AEs and SAEs
5) Record concomitant medications

5.2.3.2 Day 393 ± 7 days

1) Patient-reported outcomes assessments
   a) SGRQ-C
   b) CRQ-SAS
   c) MMRC Dyspnea Scale
   d) VAS symptom scores
2) PRO-Q
3) Perform physical examination
4) Measure weight
5) Perform 12-lead ECG (one ECG recording required)
6) Perform disease activity assessments
   a) Review the daily and weekly medication assessment as recorded in the subject's eDiary
   b) Perform 6 Minute Walk Test
   c) Assessment of AECOPD
   d) Collect health resource utilization data
7) Perform pulmonary function tests

a) Lung volumes
b) Spirometry pre- and post-bronchodilator
c) Supplemental O_2 status
d) Measure SpO_2
e) FeNO (optional)
f) DLCO

8) Collect blood for:
   a) Serum chemistry
   b) Hematology
   c) MEDI-563 serum concentration
   d) Anti-MEDI-563 antibodies
9) Collect for urine for urinalysis and a urine pregnancy test; ensure pregnancy test result is negative
10) Assessment of AEs and SAEs
11) Record concomitant medications
12) Take vital signs
13) Provide Symbicort® or Spiriva® product for daily administration, Bricanyl® as reliever (rescue) medication, and instructions for use

5.2.3.3 Day 477 ± 7 days

1) Patient-reported outcomes assessments
   a) SGRQ-C
   b) CRQ-SAS
   c) MMRC Dyspnea Scale
   d) VAS symptom scores
2) PRO-Q
3) Perform physical examination
4) Perform 12-lead ECG (one ECG recording required)
5) Perform disease activity assessments
   a) Review the daily and weekly medication assessment as recorded in the subject's eDiary
   b) Assessment of AECOPD

c) Collect health resource utilization data

6) Perform pulmonary function tests
   a) Spirometry pre- and post-bronchodilator
   b) Supplemental O_2 status
   c) Measure SpO_2
7) Collect blood for:
   a) Serum chemistry
   b) Hematology
   c) MEDI-563 serum concentration
   d) Anti-MEDI-563 antibodies
   e) Biomarker analysis
   f) Theophylline level (if applicable)
8) Collect for urine for urinalysis and a urine pregnancy test; ensure pregnancy test result is negative
9) Assessment of AEs and SAEs
10) Record concomitant medications
11) Take vital signs
12) Provide Symbicort® or Spiriva® product for daily administration, Bricanyl® as reliever (rescue) medication, and instructions for use

5.2.4 Day 561 ± 7 days: End of Study Visit/Early Discontinuation Visit

1) Patient-reported outcomes assessments
   a) SGRQ-C
   b) CRQ-SAS
   c) MMRC Dyspnea Scale
   d) VAS symptom scores
2) PRO-Q
3) Perform physical examination
4) Perform 12-lead ECG (one ECG recording required)
5) Perform disease activity assessments
   a) Review the daily and weekly medication assessment as recorded in the subject's eDiary

b) Assessment of AECOPD

c) Collect health resource utilization data

6) Perform pulmonary function tests

a) Spirometry pre- and post-bronchodilator

b) Supplemental O_2 status

c) Measure SpO_2

7) Collect blood for:

a) Serum chemistry

b) Hematology

c) MEDI-563 serum concentration

d) Anti-MEDI-563 antibodies

e) Serum for total IgE and IgE FEIA

f) Biomarker analysis

g) Whole blood PAXgene for RNA

h) Theophylline level (if applicable)

8) Collect sputum for biomarker analysis and cell count

9) Collect urine for urinalysis and urine pregnancy test; ensure pregnancy test result is negative

10) Assess for AEs and SAEs

11) Record concomitant medications

12) Take vital signs

5.2.5 Subject Evaluations In the Event of an Exacerbation

Every attempt will be made to collect the following assessments in the event of a moderate-to-severe exacerbation at the time of exacerbation or within 3 days of onset and at 14 ± 3 days post-exacerbation. Hematology and biochemistry assessment will be analyzed by the local laboratory and the hematology will be reviewed by an independent physician/hospital staff member. Beta agonists will not be withheld prior to spirometry in the event of an exacerbation. If this visit coincides with a scheduled dosing visit, then the following assessments should be performed in addition, if they are not already planned.

5.2.5.1 At Time of Exacerbation

1) Patient-reported outcomes assessments
   a) Exacerbation symptom assessment based on Anthonisen definition
   b) CRQ-SAS
   c) VAS symptom scores
   d) Clinicians Global Impression (CGI) exacerbation severity
2) PRO-Q
3) Perform physical examination
4) Perform 12-lead ECG
5) Assess for AEs and SAEs
6) Record concomitant medications
7) Take vital signs
8) Perform a chest x-ray
9) Perform pulmonary function tests
   a) Spirometry
10) Collect blood for:
   a) Serum chemistry
   b) Hematology
   c) Serum and plasma for biomarker analysis
   d) Whole blood PAXgene for RNA (only at exacerbation)
11) Collect spontaneous sputum for biomarker analysis, cell count and bacterial culture
12) Collect spontaneous sputum for viral reverse transcriptase polymerase chain reaction (RT-PCR)

5.2.5.2 14 ± 3 days Post exacerbation

1) Patient-reported outcomes assessments
   a) CRQ-SAS
   b) VAS symptom scores
   c) Clinicians Global Impression (CGI) exacerbation severity
2) PRO-Q
3) AECOPD Inpatient form (for exacerbation resulting in hospitalization only)

4) Perform physical examination
5) Perform 12-lead ECG
6) Assess for AEs and SAEs
7) Record concomitant medications
8) Take vital signs
9) Perform pulmonary function tests
   a) Spirometry
10) Collect blood for:
   a) Serum chemistry
   b) Hematology
   c) Serum and plasma for biomarker analysis
11) Collect induced sputum (if possible) for biomarker analysis and cell count

5.2.6 Additional Follow up Visits (If Required)

Additional follow up visits will occur every 84 days until peripheral blood eosinophil counts return to 50 cells/µL or 20% of Day 1.

1) Collect blood for hematology (if applicable)

5.3 Description of Study Procedures

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

5.3.1 Medical History and Physical Examination, ECG, Vital Signs and Chest x-ray

This section lists the parameters of each planned study assessment. The assessments of each visit are listed in Table 5.2-1.

5.3.1.1 Medical/Surgical History

A complete medical/surgical history will be performed at screening and 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.

5.3.1.2 Physical Examination

Physical examinations will be performed as indicated in Table 5.2-1 and Table 5.2-2 by a physician and will include examination of the following: general appearance, head, ears, eyes, nose, throat (HEENT), neck, skin, cardiovascular system, respiratory system, abdominal system and nervous system. The physical examination will include height and weight measurements.

5.3.1.3 Vital Signs

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

In addition, subjects will be monitored after investigational product administration for immediate investigational product reactions for a minimum of 2 hours with vital signs taken immediately after administration of investigational product and at least every 30 minutes (± 5 minutes) thereafter or until stable, whichever is later. 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.

5.3.1.4 Pulse Oximetry

A resting transcutaneous SpO_2 measurement should be performed at designated visits (except Day 341) by means of a finger probe.

5.3.1.5 ECG

12-lead ECGs will be performed as outlined in Table 5.2-1 and Table 5.2-2. Computerized 12-lead ECG recordings will be obtained, after the subject has been supine for a minimum of 10 minutes. Each lead will be recorded for at least 3 to 5 beats at a speed of 25 mm/sec paper speed and 10 mm/mV amplitude. Heart rate, P, PR, QRS, QT and QTc intervals (msec) will be recorded from the 12-lead ECG. Three measurements will be taken at screening and pre-dose on Day 1. The mean value recorded pre-dose will be classed as baseline.

If a subject's QTc(B) interval extends beyond 500 msec or is increased more than 70 msec compared to baseline on 2 or more ECG tracings separated by at least 5 minutes then the ECG tracing should be examined and manual measurement by a trained site physician should be performed to confirm the accuracy of the equipment being used. If the reading is accurate:

- The subject should be monitored closely and followed until the QT and QTc interval returns to within 30 msec of their baseline.
- The subject should be considered for withdrawal from treatment. If a subject is withdrawn, the withdrawal procedures should be followed as in Section 5.2.4.

The digital ECG data will be acquired and stored electronically and manually over-read by an external central validated ECG laboratory. All ECGs will be read blinded by the central laboratory. The final intervals and morphology analyses entered into the data base will be those generated by the central ECG laboratory.

5.3.1.6 Chest x-ray or CT Scan

If required, a chest x-ray or CT scan will be completed during the screening period and if indicated at each exacerbation visit. The chest x-ray or CT scan may be substituted with documentation of a previous chest x-ray or CT scan performed within the previous 12 months that meets inclusion criteria.

5.3.2 Clinical Laboratory Tests

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

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

Serum Chemistry

- Bicarbonate
- Calcium
- Chloride
- Magnesium
- Potassium
- Sodium
- Aspartate transaminase (AST)
- Alanine transaminase (ALT)
- Alkaline phosphatase (ALP)
- Gamma glutamyl transferase (GGT)
- C-reactive protein (CRP)
- Lactic dehydrogenase (LDH)
- Blood urea nitrogen (BUN)
- Uric acid
- Creatinine
- Total bilirubin
- Glucose
- Albumin
- Total protein
- Triglycerides (fasting for at least 8 hours and at screening only)
- Cholesterol (fasting for at least 8 hours and at screening only)
- Creatine phosphokinase (CPK)
- FSH (for postmenopausal females at screening only)

Hematology*

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hematocrit
- Hemoglobin
- Platelet count
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)
- Sedimentation rate/Plasma Viscosity (to be done at local laboratory)

* Hematology will be collected for local (Day -56) and central laboratory analysis

Urinalysis

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

Pregnancy Test (females of childbearing potential only)

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

Other Safety Tests

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

- Parasite serology and stool sampling (if applicable via local lab)
- Creatine phosphokinase isoform MB (CPK-MB) will only be done if CPK is raised
- Cardiac Troponin I will be done if CPK is raised more than 3 times the upper limit of normal
- Serum tryptase
- Theophylline level (if applicable)
- TB test if applicable, as per local standard of care guidelines

Other Tests

- Serum IgE
- Serum IgE FEIA to common aeroallergens
- Sputum bacterial cultures in the event of an exacerbation
- Sputum viral for RT-PCR in the event of an exacerbation

5.3.3 Pneumococcal and Annual Influenza Vaccination

Subjects will be required to have a pneumococcal vaccination if they have not had one before. In the event that they have previously received a vaccination, the Investigator must ensure that the subject does not require a booster. If a booster is required, it must be given.

Subjects will receive an annual influenza vaccination in the autumn or winter period unless the subject has received it prior to study start. If the subject has previously received the influenza vaccination within the last 12 months prior to study start, the vaccination must be given at the next autumn or winter period. If a subject has an egg intolerance, the vaccination may be omitted.

Influenza vaccination should not be given within 3 weeks of a scheduled sputum collection. The vaccination can be administered after sputum collection has been completed.

5.3.4 Pharmacokinetic Evaluation and Methods

Blood samples for MEDI-563 concentration determination will be collected as indicated in Table 5.2-1. When investigational product is administered, PK samples will be collected pre-dose and 1 hour post-dose. Instructions for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to the sites.

5.3.5 Immunogenicity Evaluation and Methods

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

5.3.6 Biomarker Evaluation and Methods

5.3.6.1 Serum/Plasma Biomarkers

Serum and plasma samples will be collected according to the schedule of study procedures to assess serum biomarkers of eosinophil and basophil activation, eosinophil and basophil growth factors, eosinophil recruitment, and inflammation associated with COPD including but not limited to cytokines, chemokines acute phase response proteins, fibrinogen, serum-amyloid A, procalcitonin, IL-8, vitamin D, and other inflammatory mediators.

5.3.6.2 Sputum Biomarkers

Sputum will be collected and processed using a modification of a previously published method (Pizzichini et al, 1998; McCormick et al, 2007) to provide a minimum of 70 mg of sputum plugs. Sputum supernatants will be collected according to the schedule of study procedures to assess sputum cell counts and sputum biomarkers of eosinophil and basophil activation, eosinophil and basophil growth factors, eosinophil recruitment, and inflammation associated with COPD including but not limited to cytokines, chemokines acute phase response proteins, and other inflammatory mediators.

5.3.6.2.1 Spontaneous Sputum for Bacterial Cultures

A sample of spontaneous sputum collected during AECOPD will be used for assessment of presence of pathogenic bacteria by culture. The analyses will be completed locally at the site's microbiology laboratory.

5.3.6.2.2 Spontaneous Sputum for Viral RT-PCR

A sample of spontaneous sputum will be used for assessment of viral load by RT-PCR. These samples will be processed according to the laboratory manual and will be shipped to a central lab for assessment.

5.3.6.3 RNA Transcript Profiling

PAXgene whole blood samples will be collected as indicated in Table 5.2-1 and Table 5.2-2 for whole genome RNA transcript analysis. The purpose of these analyses will be to retrospectively evaluate whole blood transcript biomarkers predictive of subject response at baseline, prior to investigational product administration as well as to potentially identify additional pharmacodynamic biomarkers.

5.3.6.4 Safety Biomarkers

A serum samples will be collected for baseline assessment of serum tryptase on Day 1.

In addition, if an anaphylactic reaction occurs during or within a 24-hour period after administration of investigational agent, whole blood for assessment of serum tryptase will be collected as soon as possible after the subject has been stabilized, and 1-2 hours after the event. In addition, hematology and serum chemistry, including CPK and CRP will be measured at the same time points.

5.3.7 Disease Evaluation and Methods

5.3.7.1 Assessment of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Subjects are instructed about exacerbations and when and how to call the clinic if their symptoms have changed or if they have any reason to believe they are becoming sicker and need medical attention.

The severity of an exacerbation of COPD is defined as:

- Mild exacerbations require treatment with an increase in usual therapy, eg, increase use of short acting bronchodilators
- Moderate exacerbations require treatment with systemic corticosteroids, and or antibiotics
- Severe exacerbations require hospitalization.

Subjects will be instructed to do the following when changes in symptoms and exacerbations occur:

- Increase their Bricanyl® usage for relief of symptoms.

- Contact the investigator immediately and report to the clinic as soon as possible **(and within 3 days)** if there is no satisfactory relief.

In the event of a moderate-to-severe exacerbation, every attempt will be made to collect the assessments described in Table 5.2-2.

On contact from the subject, the study site will confirm the exacerbation onset by administering a brief exacerbation assessment based on the Anthonisen (Anthonisen et al, 1987) definition of an AECOPD: worsening of 2 or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of any one major symptom together with any one of the following minor symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or wheeze for at least 2 consecutive days (Anthonisen et al, 1987).

It may be necessary for a subject to attend a hospital (or see a healthcare professional) that is not involved with the study, in which case it may not always be possible for a subject to report to the study site within the 3 day window.

Duration of an AECOPD is defined as the length of time (days) between day of onset and recovery. Recovery is the point at which a subject experiences sustained improvement in their event, with a decrease in EXACT score ≥ 9 points from the maximum observed value (MOV) on any subsequent day during the observational period. The first of the 7 consecutive days of improvement is designated the first day of recovery.

A relapse of AECOPD is defined as a worsening of AECOPD symptoms after an initial improvement but prior to achieving a stable chronic COPD treatment regimen for a minimum of 14 days and requiring re-treatment with systemic corticosteroids, or hospitalization. For the purposes of this study, a relapse of AECOPD would not be considered to be the same as a new episode of AECOPD as regards to the analysis of the rate of AECOPD (Aaron et al, 2002). It should be noted that a subject may not return to their previous level of function after resolution of an episode of AECOPD.

Study investigators or study personnel will assess the severity of the worsening symptoms to determine the need for additional treatment. If additional treatment beyond blinded investigational product or short-acting bronchodilators is required, investigators will treat the exacerbation with a course of antibiotics and/or systemic corticosteroids as deemed necessary. Subjects will be treated with a course of systemic corticosteroids, not to exceed 14 days, unless given approval by the study sponsor. A course of antibiotics will be given for

approximately 10 days in duration or according to local clinical guidelines. Additional courses may be prescribed if the first line treatment failed. Use of antibiotics for treatment of upper or lower respiratory tract infections will not be considered an exacerbation unless accompanied by worsening symptoms of COPD. Any course of antibiotics or systemic corticosteroids starting within 7 days of the stop date for a previous course will not be considered treatment of a new exacerbation.

Besides subject-reported AECOPD episodes, frequency of AECOPD will also be assessed using the EXACT-PRO score change for unreported AECOPD episodes defined as: an increase of 12 points above the subject's mean baseline for 2 consecutive days OR on increase of 9 points above subject mean baseline for 3 consecutive days.

5.3.7.2 Pulmonary Function Tests

All equipment must be calibrated on regular basis.

5.3.7.2.1 Office Spirometry Pre- and Post-bronchodilator

COPD evaluations will be assessed via airflow limitation (spirometry with FVC, FEV_1, FEV_1/FVC). Spirometry pre- and post- albuterol/salbutamol (4 puffs) or equivalent dose of other inhaled short acting β2-agonist will be performed at study sites by the investigator or qualified designee according to American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines (Miller et al, 2005) at designated visits.

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

- Short-acting β2-agonists for at least 6 hours including reliever medication
- Long-acting β2-agonists and caffeinated food products including caffeinated drinks for at least 12 hours
- Any medication containing ephedrine/pseudo-ephedrine for at least 48 hours

Subjects should observe the following restrictions prior to the clinic lung function tests:

- No smoking within 1 hour
- No alcohol within 4 hours
- No vigorous exercise within 2 hours
- No large meals within 2 hours

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

Subjects should be sitting during spirometry testing, however, if the subject is obese (body mass index [BMI] ≥ 40), or 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 (Hankinson et al, 1999) will be recorded. The highest FVC will also be reported regardless of the effort in which it occurred (even if the effort did not result in the highest FEV_1). Nose clips will be used for office spirometry.

The print-outs from the lung function measurements must be signed, dated, and marked with study code, subject identification number, date and time of measurement, visit number, and subject initials and must be filed in the subject's medical records. The results from each spirometry assessment will be entered onto the eCRF by site personnel.

5.3.7.2.2 Lung Volumes

Lung volume subdivisions which include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC) will be performed at study sites by the investigator or qualified designee according to ATS/ERS guidelines (Wanger et al, 2005) according to the study schedule. Lung volumes will be determined by body plethysmography. The test will be performed by qualified pulmonary function technicians with experience performing this study. At least 3 FRC values that agree within 5% (ie, the difference between the highest and lowest value divided by the mean is ≤ 0.05) should be obtained and the mean value reported.

5.3.7.2.3 Diffusion Capacity for Carbon Monoxide (DLCO)

Diffusion capacity for carbon monoxide will be performed at study sites by the investigator or qualified designee according to ATS/ ERS guidelines (MacIntyre et al, 2005) according to

the study schedule. The single breath technique will be used to determine the DLCO. The test will be performed by qualified pulmonary function technicians with experience performing this study. Acceptable test criteria include an inspiratory volume of more than 85% of VC; a stable breath hold of 10 ± 2 seconds with no leaks, Valsalva or Mueller maneuvers; and expiration in less than 4 seconds with appropriate clearance of dead space. The average of the two best acceptable maneuvers will be used. There must be a minimum of 4 minutes between the performance of each test.

5.3.7.2.4 Fraction of Exhaled Nitric Oxide (FeNO)

This test is optional for the site if the equipment is not available. Airway inflammation will be evaluated using a standardized single-breath FeNO (ATS, 2005) test. Since spirometry can potentially impact the nitric oxide (NO) measurement, the FeNO test needs be completed prior to spirometry. In addition, subjects should not eat or drink 1 hour prior to having the FeNO, as this may affect the results.

A seated subject inspires medical compressed air from a reservoir connected to a mouthpiece fitted with a 2-way valve. After inspiration to total lung capacity, the subject exhales immediately at a constant flow rate. The exhaled air will be collected via a side port close to the mouth and analyzed online for NO content using an instrument calibrated with NO gas standard. Three acceptable measurements are taken with at least 30 seconds of relaxed tidal breathing between maneuvers. The mean reading of the 3 results will be used for analysis. The NO equipment from each study center will be calibrated per the equipment manufacturer recommendation.

5.3.7.2.5 Sputum Induction

Sputum will be induced and collected to better understand the effect of MEDI-563 on eosinophils in sputum and to correlate the results with eosinophilic phenotype.

Sputum will be induced and analyzed in subjects as described by Pizzichini (Pizzichini et al, 1996). Subjects should not use the following prior to sputum induction:

- Short-acting β2 agonists for at least 6 hours
- Long-acting β agonists for at least 12 hours
- Leukotriene modifiers for at least 24 hours prior to the visit
- Xanthine-containing derivatives for at least 12 hours prior to the visit.

- Any medication containing ephedrine/pseudo-ephedrine for at least 48 hours

The post bronchodilator spirometry measurement must be done as per protocol prior to sputum induction (See Section 5.3.7.2.1). These measurements will be used for safety reference. If the FEV_1 after inhalation of the short-acting β2-agonist is less than 1.0 L, the procedure will not continue and spontaneous sputum will be collected for these subjects.

The subject will sequentially inhale 3%, 4%, and 5% saline for 5 minutes each. After 5 minutes, the subject will be asked to rinse their mouth and throat with water and to blow their nose in order to reduce squamous cell contamination and postnasal drip. The subject will be asked to attempt to cough and produce a sputum sample. Several attempts at coughing should be made until the sound of the cough becomes dry and unproductive.

One FEV_1 measurement will be obtained prior to and after each saline nebulization. If the FEV_1 has fallen by more than 10% or 200 mL (whichever is greater) but less than 20% or 400 mL (whichever is greater), repeat the nebulisations with unchanged concentration of saline. Subjects should not breathe saline for > 15 minutes in total.

If the FEV_1 falls by more than 20% or 400 mL (whichever is greater) of the best post-bronchodilator value, or if significant symptoms occur, the nebulisation will be stopped and the subjects will be treated with repeat short-acting β2-agonist.

The sample must be inspected and preferably contain mucoid ("stringy") sputum, with visible opaque plugs, rather than clear, runny/frothy saliva.

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

For subjects who do not qualify for induced sputum; ie, a post-bronchodilator $FEV_1 < 1$ L, spontaneous sputum will be collected.

In the event that a subject becomes wheezy and develops chest discomfort, the inhalation of saline should be stopped, and Bricanyl® Turbuhaler® (at starting dose if 2 puffs x 0.5 mg Bricanyl® Turbuhaler®; 1 mg), or another inhaled short-acting β2-agonist at an equivalent dose, should be given.

5.3.8 Patient-Reported Outcomes (PRO)

All patient-reported outcomes should be completed prior to any clinical assessments during study visits.

5.3.8.1 COPD-Specific Saint George's Respiratory Questionnaire (SGRQ-C)

Overall health status of subjects with airway obstructive diseases will be assessed with the COPD-specific Saint George's Respiratory Questionnaire (SGRQ-C), a 40-item patient-reported outcome (Jones et al, 1991; Meguro et al, 2007). Responses include yes or no, and 3- to 5-point scales assessing the impact of symptoms, activities, and impact on daily life. Total scores and domain scores (symptoms, activities, and impact on daily life) are scored from 0-100, where lower scores indicate better health status. A 4-point change in total score has been demonstrated to be a clinically meaningful change, while an 8-point change and a 12-point change are interpreted as a moderate and large change in health status, respectively (Jones and Bosh, 1997).

5.3.8.2 Symptom Diary

5.3.8.2.1 Exacerbations of Chronic Pulmonary Disease Tool - Patient-Reported Outcomes

The Exacerbations of Chronic Pulmonary Disease Tool (EXACT) is a patient-reported outcome measure designed to standardize the measurement approach for evaluating the frequency, severity, and duration of acute exacerbations in patients with COPD, including subjects with chronic bronchitis, in international studies and clinical trials (Jones and Higenbottam, 2007). The EXACT-PRO is a 14-item daily diary to be completed by the patient on a personal digital assistant (PDA) each evening before bedtime. The 14 items have 3 to 6 response options and are scored as a total score, as three domains consisting of breathlessness (5 items), cough and sputum (2 items), chest symptoms (3 items), and 4 single items assessing difficulty with sputum, tired or weak, sleep disturbance and psychological state. Final scores range from 0 to 100, where a higher score indicates a more severe condition.

The Total score is used to determine frequency, severity and duration of exacerbation (UBC 2009).

Use of the EXACT will require the subject to establish a baseline while clinically stable. Seven days of recording will be required to establish a baseline for comparison.

5.3.8.2.2 Other Assessments in the Diary

Besides the EXACT-PRO, the following items will be assessed in the daily eDiary: rescue medication use (yes/no and the amount) in the past 24 hours, taking Symbicort® or Spiriva® in the morning (yes/no), and taking Symbicort® or Spiriva® in the evening (yes/no). Detailed questions that will be asked in the eDiary will be described in the Study Manual.

5.3.8.3 Chronic Respiratory Questionnaire (CRQ)

The chronic respiratory questionnaire (CRQ), a widely used measure of health-related quality of life (HRQOL) in patients with chronic airflow limitation, includes an individualized dyspnea domain (Guyatt et al, 1987). Subjects identify five important activities, and report the degree of dyspnea on a 7-point scale. The original CRQ was designed to be interviewer administered questionnaire. The patient self-administered standard version of CRQ (CRQ-SAS) has been validated (Williams et al, 2001) and will be administered in this study. The CRQ, and the subsequent CRQ-SAS, is made up of four dimensions relating to dyspnea, emotional function, fatigue, and mastery. There are 20 questions in total and for every question there is a range of responses that score from 1 to 7. The dimensions include fatigue, emotional function, and mastery, which are scored from 1 to 7. In each dimension the lower the score, the greater the degree of dysfunction.

5.3.8.4 Exacerbation Symptom Assessment Based on Anthonisen Definition

Once subjects have contacted the study site due to an increase in COPD symptoms that are not relieved by an increase in Bricanyl® usage; the study site will assess the subjects' exacerbation symptoms using the major and minor symptoms based on the Anthonisen definition. Major symptoms include dyspnea, sputum purulence, and sputum volume; and minor symptoms include cough/wheeze, fever, sore throat, and cold (nasal discharge/congestion) (Anthonisen et al, 1987). Dyspnea, sputum purulence and volume, and cough/wheeze will be evaluated relative to their usual state while others will be evaluated based on their absence or presence for the past 2 days. Subjects will rate their symptoms using a 3-point scale.

A COPD exacerbation will be defined as worsening of two or more major symptoms or one major and one minor symptom for two or more consecutive days (Anthonisen et al, 1987). The study investigator or coordinator will confirm a subject's exacerbation and schedule the subject to report to their study site as required for evaluation.

5.3.8.5 Visual Analogue Scale (VAS)

The perception of symptoms severity will be measured using a VAS. The VAS is a 100 mm length line where subjects will simply mark on the line how they feel from no symptoms to worst ever symptoms. This will be measured using a ruler. VAS will be used to assess symptom severity of dyspnea, cough, and sputum production and sputum purulence.

5.3.8.6 Modified Medical Research Council (MMRC) Dyspnea Scale

MMRC dyspnea scale comprises 5 statements that describe almost the entire range of respiratory disability from none ("no trouble with breathlessness except with strenuous exercise"; Grade 1) to almost complete incapacity ("too breathless to leave the house or breathless when dressing or undressing"; Grade 5: Stenton 2008).

5.3.9 Patient-Reported Outcomes Questionnaire Study Coordinator Form (PRO-Q)

Upon subjects' completion of the patient-reported outcomes assessments, the study coordinators will complete a PRO-Q which documents whether the study subject completes the PRO assessments for the visit, the reason for non-completion, whether the study subject requires assistance for completing the form and from whom the assistance was from.

5.3.10 Clinical Global Impression of Exacerbation Severity

Clinicians will complete a CGI of Exacerbation Severity assessment when subjects are evaluated for their AECOPD. The assessment is on a 4-point scale as follows:

- 0 = "no exacerbation"
- 1 = "mild exacerbation"
- 2 = "moderate exacerbation"
- 3 = "severe exacerbation"

5.3.11 Functional Assessment - Six Minute Walk Test

Walking is an activity performed daily by all but the most severely impaired patients. The 6MWT measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems. The self-paced 6MWT assesses the submaximal level of functional capacity.

5.3.12 BODE Index

The **B**ody-Mass Index, Airflow **O**bstruction, **D**yspnea, and **E**xercise Capacity (BODE) index is calculated for classification of COPD. The score comprises BMI, post-bronchodilator FEV_1% predicted, grade of dyspnea (measured by the modified MMRC dyspnea scale) and the six-minute-walking distance (Celli et al, 2004). The BODE index ranges from 0-10 points with higher score indicating worse outcome. Four severity stages represent BODE index scores: BODE stage I = BODE index 0-2; BODE stage II = BODE index 3 and 4; BODE stage III = BODE index 5-7; and BODE stage IV = BODE index 8-10.

The BODE Index will be calculated from the above measurements on Day 1, Day 113, and Day 393.

5.3.13 Health Resource Utilization

Information will be collected by study site coordinator from either the subject's medical chart and/or from study subject at each study visit during the study to quantify the impact of disease and treatment on the subject's health resource utilization (HRU). Information collected will include COPD -related medical encounters and exacerbation- (that does not result in hospital stay) related medical encounters (ie, phone calls to healthcare providers, physician office/outpatient visits, emergency room visits, hospitalizations, intensive care unit stays, and ventilator use), home treatment, and medications and changes. For exacerbations that result in hospital stay, the AECOPD Inpatient form will be used.

5.3.14 AECOPD Inpatient Assessment

Information will be collected by study site coordinator from either the subject's medical chart and/or from study subject at Day 14 ± 3 days post-exacerbation (or post-exacerbation study

visit) regarding the exacerbations that result in hospital stay. Information collected will include length of stay for hospitalizations, intensive care unit stays, and ventilator use, reasons for hospital admission, co-morbid diseases treated, discharge information (date, destination and criteria), and relapse.

5.3.15 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 Day 561, and the estimated volume of blood to be collected at each visit at the time of an AE and 7-10 days after an AE are presented in Table 5.3.15-1.

Table 5.3.15-1 Estimated Volume of Blood to be Collected per Visit up to Day 561

Visit	Estimated Blood Volume (mL)
Day -56	28
Day -28	0
Day 1	65 (69) [a]
Day 29	24
Day 57	54
Day 113	35 (39) [a]
Day 169	27
Day 225	65 (69) [a]
Day 281	27
Day 337	27 (31) [a]
Day 341	5.0
Day 393	27
Day 477	55 (59) [a]
Day 561	65 (69) [a]
Overall Total (screening to Day 561)	504 (528) [a]
At the time of an AECOPD and approximately 14 days post AECOPD	40 mL per visit
Additional follow up visits (if applicable)	4 mL

[a] Includes an additional 4 mL blood volume for theophylline level if applicable

6 Assessment of Safety

6.1 Safety Parameters

6.1.1 Adverse Events

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

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

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. 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 non-treatment emergent. A non-treatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

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

6.1.2 Serious Adverse Events

A serious adverse event (SAE) is any AE that:

- Results in death
- Is immediately life-threatening

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

- Requires inpatient hospitalization or prolongation of existing hospitalization

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

- Results in persistent or significant disability/incapacity

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

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

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

6.2 Assessment of Safety Parameters

6.2.1 Assessment of Severity

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

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5 (fatal)	Death (loss of life) as a result of an event.

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

6.2.2 Assessment of Relationship

6.2.2.1 Relationship to Investigational Product

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

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

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

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

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

6.2.2.2 Relationship to Protocol Procedures

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

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

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

6.3 Recording of Safety Parameters

6.3.1 Recording of Adverse Events and Serious Adverse Events

Adverse events will be recorded on the 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 6.1.2 for the definition of SAEs, and Section 6.2.1 and Section 6.2.2 for guidelines for assessment of severity and relationship, respectively. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

6.4 Reporting Requirements for Safety Parameters

6.4.1 Study Reporting Period and Follow-up for Adverse Events

The reporting period for AEs is the period immediately following the time that written informed consent is obtained through the end of subject participation in the study. New (non-serious) AEs that start after the reporting period will not be collected.

All AEs will be followed to resolution through the end of subject participation in the study, even if the date extends beyond the reporting period.

6.4.2 Reporting of Serious Adverse Events

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

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

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

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

6.4.2.2 Notifying the Sponsor of Serious Adverse Events

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

MedImmune contact information:

Patient Safety
MedImmune
One MedImmune Way
Gaithersburg, MD 20878
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 (see Section 6.4.2.3). The sponsor may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the sponsor as soon as it becomes available.

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

6.4.2.3 Safety Reporting to Investigators, Institutional Review Boards or Independent Ethics Committees, and Regulatory Authorities

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

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

For all other investigators, the sponsor will prepare an expedited report for all SAEs that are unexpected and potentially related to the investigational product, and copies will be distributed to all concerned regulatory authorities, investigator(s), and IRBs/IECs according to applicable laws and regulations. The investigational site also will forward a copy of all expedited reports to the site's applicable IRB/IEC. Investigators must also submit safety information provided by the sponsor to the IRB/IEC as detailed in Section 10.1 and Section 10.2.

6.4.3 Other Events Requiring Immediate Reporting

6.4.3.1 Overdose

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

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

6.4.3.2 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 Fax Notification Form (see Section 6.4.2.2 for contact information).

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

6.5 Safety Management During the Study

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

The medical monitor and patient safety physician will meet no less than on a quarterly basis to review the blinded safety data, which will include but is not limited to laboratory data listings, clinical listings of AEs and SAEs, subject history and concomitant medications.

The MedImmune SMC will review safety data on a regular basis throughout the study and make recommendations regarding further conduct of the study if required. At any time during the study, the MedImmune SMC will also review safety data assessed by the medical monitor as medically relevant.

7 Statistical Considerations

7.1 General Considerations

All data related to various study endpoints will be displayed in data listings sorted by treatment group (MEDI-563 100 mg and placebo), subject number, and study visit for unblinded analysis. Summary data will be presented in tabular format 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 N, mean, standard deviation (SD), median, minimum, and maximum. Confidence intervals (CIs)

will be 2-sided, unless otherwise stated. Details of endpoint analyses will be described in a comprehensive SAP.

7.2 Analysis Populations

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

The Per-Protocol (PP) Population includes all subjects who have no major protocol violations, have received at least 6 of the 8 total doses (at least 2 of the first 2 doses on Days 1 and 29, and at least 4 of the last 6 doses on Days 57, 113, 169, 225, 281, and 337) of investigational product, and have completed the study through Day 393. The PP Population will be identified prior to database lock (ie, prior to restricting access to the clinical study database after known data processing activities are complete).

The Safety Population includes all subjects who receive at least one dose of investigational product.

The Evaluable Population for PK will include all subjects who receive at least one dose of investigational product and have a sufficient number of serum concentration measurements for computing PK parameters. The Evaluable Population for IM will include all subjects who receive at least one dose of investigational product and have at least one serum sample for IM testing.

The safety and PK/IM analyses will be presented on an as treated basis. Some imputation maybe used in the primary endpoint analyses. All other missing data will be treated as missing without data imputation.

7.3 Endpoints

7.3.1 Primary Endpoint

The primary objective of this study is to evaluate the effect of multiple SC doses of MEDI-563 on the rate of moderate-to-severe AECOPD in adult subjects with moderate-to-severe COPD as defined in Section 5.3.7.1. The primary endpoint will be the number of

moderate-to-severe AECOPD experienced by subjects after their first dose of investigational product to their Day 393/Early Discontinuation visit.

A Van Elteren test will be performed for testing the differences in number of moderate-to-severe AECOPDs between the MEDI-563 treatment group and the placebo group. The Van Elteren test is a stratified Cochran-Mantel-Haenzel (CMH) Row Mean Scores test, which is the equivalent to Kruskal-Wallis test when the comparison is performed between the MEDI-563 treatment group and the placebo group without involving other stratification factor(s). The two-sided test will be conducted over the PP Population and will constitute the primary analysis for which this study is powered.

The mean rate of moderate-to-severe exacerbations based on PP Population will also be evaluated with a Poisson regression model and a Negative binomial model. An overdispersion parameter will be used to adjust for variability in the data for Poisson regression model.

To check the sensitivity of the comparisons, the above analyses will be repeated over the ITT population.

7.3.2 Secondary Endpoints

Listing of vital signs and ECGs will be generated. Laboratory measurements will be evaluated as changes from baseline at each collection time point. Adverse events and SAEs will be summarized categorically by system organ class, preferred term, severity, and relationship to investigational product.

The number and proportion of subjects that are hospitalized due to moderate-to-severe AECOPD will be summarized by treatment group. The annual rate of hospitalization due to moderate-to-severe AECOPD may be compared between the MEDI-563 group and the placebo group using a Poisson regression model with an overdispersion parameter to adjust for variability in the data.

A summary of baseline score and changes from baseline will be performed for the SGRQ-C. The absolute change value as well as the proportion of subjects with a 4-point change (improvement), an 8-point change, and a 12-point change in total scores will be tabulated by treatment group.

A summary of baseline score changes from baseline will be performed for the CRQ-SAS. The proportion of subjects with a 0.5-point change (improvement) in each dimension will be tabulated by treatment group.

Both BODE Index and MMRC scale will be tabulated by treatment group. A shift table may be produced.

7.3.3 Exploratory Endpoints

The exploratory objectives of this study are:

1) To assess the effect of MEDI-563 on the time to first moderate-to-severe AECOPD
2) To assess the number of subjects who exhibit at least one moderate-to-severe AECOPD
3) To assess the effect of MEDI-563 on the number of exacerbation free days as measured by the EXACT-PRO
4) To assess the effect of MEDI-563 on the number, duration and severity of moderate-to-severe AECOPD as measured by the EXACT-PRO
5) To assess the effect of MEDI-563 on pulmonary function as assessed by changes from baseline in FEV_1
6) To describe the effect of MEDI-563 on functional performance, measured by 6MWT
7) To describe the PK and IM of MEDI-563 in COPD subjects
8) To assess the effect of MEDI-563 on dyspnea symptom as measured by the MMRC Dyspnea Scale
9) To assess the effect of MEDI-563 on symptom scores as measured by VAS. Symptom scores include cough, breathlessness, sputum purulence and sputum production.
10) To assess the effect of MEDI-563 on the use of concomitant medications
11) All-cause mortality in the 1 year post-randomization amongst all subjects randomized to treatment
12) To evaluate the effect of MEDI-563 on blood and sputum biomarkers
13) To assess the effect of MEDI-563 on healthcare resource utilization and economics
14) To assess the effect of MEDI-563 on total serum IgE and IgE FEIA for common aeroallergens
15) To develop and test clinical prediction rules (diagnostic tools) for discriminating COPD phenotypes

A log-rank test will be conducted to compare the time to first moderate-to-severe AECOPD between the MEDI-563 group and placebo group. A proportional hazard model may be used to explore the effect of some covariates. If enough data are available to compute a median, the median for the time to first AECOPD along with a 95% confidence interval will be estimated by using Kaplan-Meier method.

The number and proportion of subjects who exhibit at least one moderate-to-severe AECOPD will be summarized by treatment group. The Fisher's exact test will be carried out to compare the proportion of subjects who exhibit at least one moderate-to-severe AECOPD between the MEDI-563 group and placebo group.

The number of exacerbation-free days and the proportion of exacerbation-free days as measured by the EXACT-PRO will be tabulated by treatment group.

The rate of moderate-to-severe AECOPD as measured by the EXACT-PRO will be compared between the MEDI-563 group and the placebo group using the Van Elteren test and using a Poisson regression model with an overdispersion parameter to adjust for variability in the data. Exacerbation duration, defined as the length of time (days) between day of onset and recovery, will be analyzed using a repeat measure analysis of covariance.

Descriptive statistics (Mean, standard deviation, minimum, and max, etc.) of changes from baseline in FEV_1 will be provided.

The 6MWT measures the distance that a subject can quickly walk on a flat, hard surface in a period of 6 minutes. Descriptive statistics of baseline value and change from baseline will be provided by treatment group.

Changes in the perception of symptoms severity will be measured using a VAS assessment. The baseline score absolute value at each visit as well as the changes from baseline will be summarized by treatment group.

The PK and IM of MEDI-563 will be evaluated. Individual MEDI-563 serum concentrations will be tabulated by treatment group along with descriptive statistics. Non-compartmental PK data analysis will be performed for MEDI-563 treated subjects and descriptive statistics of these non-compartmental parameters will be provided.

Descriptive statistics for concomitant medication use, mortality rate in the one-year post-randomization and health resource utilization will be provided by treatment.

The IgE FEIA and CRP values will be evaluated in the MEDI-563 and placebo groups as changes from baseline. The analyses will be primarily descriptive. Two sample t-tests may be used to compare the change from baseline for some continuous exploratory endpoints between the combined MEDI-563 and placebo groups. By subject measurement-time profile plots stratified by treatment groups may be created to explore the variation of some exploratory endpoints such as eosinophil counts in peripheral blood within subjects. Details of the analyses will be provided in the statistical analysis plan.

Total serum IgE levels may be increased in eosinophilic COPD subjects relative to healthy controls. In addition, elevated numbers of eosinophils in peripheral blood may be increased in COPD. Blood and sputum eosinophil levels will be correlated to clinical parameters and serum IgE levels. Descriptive statistics will be used to summarize the results.

Multivariate statistical procedures will be used, primarily on data collected at the screening visit (to include both screen failures and subjects who get randomized) with an aim to develop and statistically validate useful clinical prediction rules for discriminating COPD phenotypes (eg, eosinophilic and neutrophilic), drug-responders versus non-responders, and other sub-groups of potential interest. As this is an exploratory objective of the study, the data analysis will be carried out using a variety of data-mining techniques and statistical methods, but with an aim to maximize classification accuracy measures (sensitivity, specificity, positive predictive value, negative predictive value, and the likelihood ratios). If clinical prediction rules are developed with sufficiently high classification accuracy for potential use, such diagnostic tools will be internally cross-validated (eg, by using hold-out samples or the leave-one-out method), and CIs will be estimated using bootstrap re-sampling.

7.4 Primary Efficacy Analysis

The primary efficacy analysis will be conducted after all subjects have either completed the Day 393 evaluations or have been discontinued from the study early. The primary endpoint analysis outlined in Section 7.3.1 will constitute the analysis. Since the primary endpoint analysis for which this study is powered will be completed at the primary efficacy analysis, it will not be repeated at the end of the study. As such there is no need for multiplicity adjustment of the Type I error. Analysis of safety data available at the time of data cut-off will be presented in the primary efficacy analysis. If necessary, analyses of limited secondary endpoints may be included in the primary efficacy analysis. The primary efficacy analysis methodology and the review of the resulting data within the Sponsor will be described in the

SAP. The actual data from the primary efficacy analysis will not be communicated to personnel at the contract research organization or investigational sites or to enrolled subjects.

7.5 Sample Size and Power Calculations

Sample size and power calculations have been performed for the primary endpoint of moderate-to-severe AECOPD rate to allow hypothesis testing. Sample size and power calculations are based on the Van Elteren test (two-sided) with alpha = 0.05 for testing the difference in moderate-to-severe AECOPD rates between the MEDI-563 treatment group (100 mg) and the placebo group. Assumptions include: (1) moderate-to-severe AECOPDs evaluated through Day 393 and (2) a MEDI-563 to placebo randomization ratio of 1:1.

With 72 subjects (n=36 for MEDI-563 and n=36 for placebo), the power to detect statistically significant differences in the moderate-to-severe AECOPD rates between the MEDI-563 treatment group and the placebo group is presented in Table 7.5-1. The Van Elteren test is a stratified CMH Row Mean Score test. As there is no formal formula for calculating power using the CMH row mean score test, power calculations were performed using a simulation program.

Table 7.5-1 Power for Different Scenarios (N = 90)

Annual Exacerbation Rate in Placebo	Relative Rate Reduction	Power
2	40%	76.8%
2	50%	94.0%
1.5	40%	66.0%
1.5	50%	85.5%
1	40%	48.6%
1	50%	68.0%

Assuming a drop-out rate of about 20% in the study, a total of 90 subjects are needed for this study.

8 Direct Access to Source Documents

The study will be monitored by the sponsor on a regular basis throughout the study period. During monitoring visits, the investigator will provide direct access to all source

documentation relevant to the subject's participation in the study. Source documentation includes, but is not limited to, the subject's clinic and/or office chart, hospital chart, informed consent forms, treatment notes, laboratory reports, pharmacy records, radiographs, recorded data from automated instruments, and any other records maintained to conduct and evaluate the clinical study. The investigator must also ensure that direct access to study documents be made available for study-related audits, IRB/IEC review, or regulatory inspection.

9 Quality Control and Quality Assurance

9.1 Data Collection

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

Subject demographics and key/essential disease baseline characteristics thought to affect outcome, ie, stratification variables and other prognostic factors, will be collected, as available, for all subjects who provide written informed consent. For subjects who provide informed consent and were not entered/randomized into the study, the reason the subject was not entered/randomized, ie, did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (eg, lost to follow-up, consent withdrawn), will also be collected.

Investigator(s) must keep a record of subjects who were considered for enrolment but were never enrolled eg, subject screening log. This information is necessary to establish that the subject population was selected without bias.

9.2 Study Monitoring

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

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

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

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

9.3 Audit and Inspection of the Study

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

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

10 Ethics

10.1 Regulatory Considerations

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

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

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

10.2 Institutional Review Board or Independent Ethics Committee

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

Any documents that the IRB/IEC may need to fulfill its responsibilities, such as protocol amendments, and information concerning subject recruitment, payment, or compensation procedures, or information from the sponsor will be submitted to the IRB/IEC. The IRB/IEC's written unconditional approval of the study protocol, the informed consent form(s), and any other written materials to be provided to subjects will be in the possession of the investigator and the sponsor before the study is initiated. The IRB/IEC's unconditional

approval statement will be transmitted by the investigator to the sponsor prior to shipment of investigational product supplies to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and the date of review.

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

The IRB/IEC must be informed by the investigator of informed consent form changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study; new information that may affect adversely the safety of the subjects or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

10.3 Informed Consent

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

Information should be given in both oral and written form, and must be given ample opportunity to inquire about details of the study. Written informed consent will additionally be obtained for Subjects' consent to keep some of their blood, blood product, tissue, urine, sputum specimens that are left over from the study for future research. Subjects' specimens will not be kept for more than 15 years.

The consent form(s) generated by the investigator must be approved by the IRB/IEC and be acceptable to the sponsor. Consent forms must be written so as to be understood by the prospective subject. Informed consent will be documented by the use of a written consent form(s) approved by the IRB/IEC and signed and dated by the subject, and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form(s) must be kept on file by the investigator for possible inspection by the sponsor or its designated

monitors, auditors, or regulatory agency representatives. The subject should receive a copy of the signed and dated written informed consent form(s) and any other written information provided to the subject, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

11 Data Handling and Record Keeping

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

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

12 Financing and Insurance

Financing and insurance are addressed in the individual site contracts.

13 Publication Policy

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

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15 Summary of Protocol Amendments and Administrative Changes to the Protocol

Administrative Change 1, 13Oct2010

1) WBC counts will not be blinded throughout the study
2) E-code has been replaced with subject identification number
3) Removed height measurement from Day 1 and Day 113
4) CBC will be analyzed at Day -56 by local and central lab
5) Added text to indicate that patient-reported outcomes should be collected before any clinical assessments
6) Added text to CRQ-SAS to clarify first and follow-up administration forms
7) Added plasma viscocity (to be done at local laboratory)
8) Pro-Q was added
9) Removed ATS 2002 reference
10) Other minor text changes will be found in the body of the protocol

Protocol Amendment 1, 01Feb2011

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

1) Section 1.4 (Benefit-Risk and Ethical Assessment): Data was updated to provide clarity.
2) Section 3.1 (Overview of Study Design): Text was updated to match Inclusion Criteria where applicable and text was updated to provide clarity.
3) Section 3.3 (Study-Stopping Criteria): Text was revised to add "severe" As reflected by the literature, the spectrum of disease resulting from immune complex disease or hypersensitivity Type III could be broadly divided into 3 groups: 1.) those due to persistent infection; 2.) those due to autoimmune disease; and 3.) those caused by inhalation of antigenic material. Given the variability of clinical manifestations, the protocol was changed to address the occurrence of severe immune complex disease, in which certain types of soluble antigen-antibody complexes are not cleared by the reticulo-endothelial system, thereby depositing in blood vessel walls and into other tissues such as renal glomeruli and cause vasculitis or glomerulonephritis syndromes. Although, it is likely that a number of factors may be involved in the ultimate expression of a vasculitis syndrome or glomerulonephritis syndromes, the word

"severe" was added to immune complex disease to identify potentially the most "severe" sequelae.

4) Section 3.4.1 (Dose and Schedule Justification): Data was updated to provide clarity.

5) Section 4.2.1 (Inclusion Criteria): Inclusion Criterion 3 was revised to add "moderate to severe" and "at screening" to provide clarity. The protocol subject population is moderate and severe COPD, classified according to the GOLD criteria by a FEV_1/FVC ratio & FEV_1 predicted values.

6) Section 4.2.1(Inclusion Criteria): Inclusion Criterion 4 was revised to remove "screening" and add "Day 1" to clarify that subjects are required to be free of AECOPD for at least 8 weeks prior to receiving MEDI-563 or placebo.

7) Section 4.2.1(Inclusion Criteria): Inclusion Criterion 10 was revised to remove "or female partners". This was inadvertently added, and as it is unethical to do a FSH test on subjects that have not given informed consent, this was deleted.

8) Section 4.2.1 (Inclusion Criteria): Inclusion Criterion 11 was revised to add "or must use adequate contraception (see Table 4.2.1-1) if less than 1-year post vasectomy" to ensure female partners are protected from becoming pregnant.

9) Section 4.2.1(Inclusion Criteria): Inclusion Criterion 13 was revised to remove "screening" and add "Day 1". Subjects need to be on a stable dose of immunotherapy 90 days prior to receiving MEDI-563 or placebo. This has been amended to ensure subjects do not change their dose of immunotherapy prior to randomization.

10) Section 4.2.2 (Exclusion Criteria): Exclusion Criterion 7 was revised to add "as a primary diagnosis" and "if a subject is diagnosed with any other pulmonary disease as a secondary diagnosis, they may be included if, in the opinion of the investigator or medical monitor the inclusion does not compromise the interpretation of the study". This clarifies the criteria which allows subjects with other pulmonary diseases.

11) Section 4.2.2 (Exclusion Criteria): Exclusion Criterion 9 was revised to add "Subjects, who have epilepsy, must be on a stable dose of medication for 1 month prior to Day 1". This is added to ensure that subject do not change their medication which may result in seizures prior to dosing.

12) Section 4.2.2 (Exclusion Criteria): Exclusion Criterion 11 was revised to remove "Fever > 37.0°C (98.6°F) at screening" and add "Fever > 37.8°C (100°F) measured using tympanic temperature (or equivalent oral/rectal/axillary temperature) at Day 1". Definition of fever was updated and equipment used was added.

13) Section 4.2.2 (Exclusion Criteria): Exclusion Criterion 15 was revised to allow inclusion of subjects with hepatitis A. Hepatitis A was chosen in error and subjects with a history of Hep A will not have any increased safety risk in the study.

14) Section 4.2.2 (Exclusion Criteria): Exclusion Criterion 19 was revised to clarify TB assessments and to allow different TB assessments in different sites.

15) Section 4.2.4.1(Rescreening of Subjects): Text was updated to allow for 2 re-screenings for patients who have screen failed for HepA and who have had a moderate-to-severe exacerbation prior to or after starting the 28-day run-in period. The primary endpoint is rate of moderate-to-severe AECOPD. Agusti et al (Agusti et al, 2010) reports that previous exacerbations are the best predictor of subsequent exacerbations, thus subjects who have a mild moderate or severe exacerbation will be allowed to remain on maintenance therapy for 8 weeks prior to Day 1.

16) Section 4.3 (Treatment Assignment): Text was removed to provide clarity.

17) Section 4.4.3 (Unblinding Due to the Known Effects of MEDI-563): Removed "eosinophil counts and basophil" and added "the differential WBC". The text was revised as the entire differential WBC can unblind Investigators.

18) Section 4.5.2 (Treatment Regimens): Removed "160" as it is unknown how many screened subjects will be needed to randomize 90 subjects. As only approximately 30% of patients with COPD have elevated levels of eosinophils in the airway as measured by sputum induction or bronchoalveolar lavage (BAL; Brightling et al, 2000; 2005; Pizzichini et al, 1998; Leigh et al, 2006; reviewed in Saha and Brightling, 2006), the screening number has been removed.

19) Section 4.5.5.1 (Restriction Concomitant Medication During the Study): Updated text to provide clarity. This allows flexibility for sites to use any SABA for spirometry measurements.

20) Section 4.5.2 (Treatment Regimens) and Section 4.5.5.2 (Maintenance Therapy) Added "The start of maintenance therapy will be decided based on spirometry measurements taken at Day -56" in order to clarify which spirometry measurements were to be used to assign the maintenance therapy.

21) Section 4.5.5.4 (Allowed Concomitant Medication During the Study): Revised to add "Short courses (≤ 14 days) of medication containing oral ephedrine/pseudo-ephedrine are allowed but must be withheld 48 hours prior to a spirometry assessment (See Section 5.3.7.2.1)". Ephedrine or pseudo-ephedrine has been allowed in short courses to add flexibility to subjects who might obtain symptomatic relief with the use of medications if they have flu like symptoms.

22) Table 5.2-1 (Schedule of Study Procedures): Day -28 procedures removed are vital signs, all patient reported outcomes, PRO-Q, ECG, assessment of AECOPD, and all pulmonary function tests that require entry into the electronic database. Day -14 visit has been removed. Day 1 procedures will be used as the baseline for this study.

23) Table 5.2-1 (Schedule of Study Procedures): Text was updated to remove "Terbutaline" from Office spirometry pre- & post- bronchodilator. This allows flexibility for sites to use any SABA for spirometry measurements.

24) Table 5.2-2 (Schedule of Subject Evaluations in the Event of a Moderate-to-Severe Exacerbation): Text was revised to add "AECOPD Inpatient form (for exacerbation resulting in hospitalization only)" under 14 days post-exacerbation and remove "14 ±

2 days" and add "14 ± 3 days". This will allow the study to evaluate healthcare utilization during hospitalized AECOPD. The "14 ± 3 days" was amended to allow flexibility for subjects who exacerbate on a Friday.

25) Table 5.2-2 (Schedule of Subject Evaluations in the Event of a Moderate-to-Severe Exacerbation): Text was revised to add "if indicated" to Chest x-ray or CT scan to provide clarity.

26) Day 1, Day 28 and Day 57 visit windows were updated from "± 2 days" to "± 3 days". This was changed to allow flexibility for subjects.

27) Section 5.2.5 (Subject Evaluations In the Event of an Exacerbation): Text was revised to add "or within 3 days of onset" at time of exacerbation. This was changed to allow flexibility for subjects.

28) Section 5.3.1.3 (Vital Signs): Text was updated to remove "every visit" and add "designated visits" to provide clarity.

29) Section 5.3.1.4 (Pulse Oximetry): Text was updated to remove "every visit" and add "designated visits" to provide clarity.

30) Section 5.3.1.6 (Chest x-ray or CT Scan): Text was revised from "if possible" to "if indicated". This is to clarify at time of exacerbation a chest x-ray or CT Scan at Investigator discretion.

31) Section 5.3.7.1 (Assessment of AECOPD): Added additional clarity/language around collection of assessments during a moderate-to-severe exacerbation to eliminate unnecessary protocol violations.

32) Section 5.3.7.2.1 (Office Spirometry Pre- and Post-bronchodilator): Revised to remove "terbutaline (4 puffs)" and add "albuterol/salbutamol (4 puffs) or equivalent dose of other inhaled short acting β2–agonist". This allows flexibility for sites to use any SABA for spirometry measurements.

33) Section 5.3.7.2.1 (Office Spirometry Pre- and Post-bronchodilator): Added text "Any medication containing ephedrine/pseudo-ephedrine for at least 48 hours". This was added as pseudo-ephedrine and ephedrine is now allowed in short courses.

34) Section 5.3.7.2.5 (Sputum Induction): Text was revised to add "Any medication containing ephedrine/pseudo-ephedrine for at least 48 hours" and additional text was revised to provide clarity.

35) Section 5.3.8.5 (Visual Analogue Scale (VAS)): Text was revised to remove "wheeze" as it is not collected.

36) Addition of Section 5.3.9 (Patient-reported outcomes Questionnaire Study Coordinator form (PRO-Q)) to provide explanation on the purpose of the PRO-Q scale.

37) Section 5.3.13 (Health Resource Utilization): Text was revised to provide clarity on when the form is to be used.

38) Addition of Section 5.3.14 (AECOPD Inpatient Assessment) to provide an explanation on the purpose of the AECOPD Inpatient Assessment form.

39) Table 5.3.15-1 (Estimated Volume of Blood to be Collected per Visit up to Day 561): Volumes updated due to removal of Day -14.

Protocol Amendment 2, 15Feb2011

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

1) Section 1.4 (Benefit-Risk and Ethical Assessment): Exclude subjects if they have a history of an untreated systemic helminth parasitic infestation. Following consultation with an expert parasitologist, Dr Michael Brown, London School of Hygiene & Tropical Medicine, for most helminths in most circumstances, the disease severity associated with helminth infection is related to the number of adult worms acquired, and hence the amount of exposure, thus those with a heavy burden of infection can be rendered low risk by giving anti-helminthic treatment before study drug. Presumptive antihelminthic treatment is widely practiced in endemic settings due to the low rates of adverse events (100,000s of doses of albendazole, praziquantel and ivermectin given in helminth control programmes) and the limited predictive value of diagnostic tests.

2) Section 1.4 (Benefit-Risk and Ethical Assessment): Wording added to match exclusion criteria.

3) Section 1.4 (Benefit-Risk and Ethical Assessment): Due to the limited predictive value of serology assays, positive serologies must be confirmed by stool sampling per local guidelines if subjects test positive for *Ascaris Lumbricoides, Schistosoma Mansoni* or *Taenia Solium.* If the stool sampling is positive for *Schistosoma mansoni or Taenia solium* the subject will be excluded. All subjects with a positive serology for *Ascaris lumbricoides* will be treated with a single oral dose of 400mg albendazole. If albendazole is not licensed, the subject will be treated per local standard of care. Treatment with oral albendazole 400mg is almost 100% effective (Norhayati et al, 1997). All subjects will be treated with albendazole if tested positive for serology. The reason being that eggs do not appear in the stool for at least 40 days after infection; thus an early diagnosis, including during the phase of respiratory symptoms, cannot be made if the sole diagnostic marker is reliance upon eggs in feces. In addition, no eggs will be present in stool if the infection is due to male worms only.

4) Section 3.1 (Study Design): Wording added to include stool sampling (if applicable).

5) Section 4.2.2 (Exclusion Criteria): Exclusion Criterion 16 changed to exclude a history of an untreated systemic helminth parasitic infestation.

6) Section 4.2.2 (Exclusion Criteria): Exclusion Criterion 16 divided into two separate criterions for clarification to distinguish the history of parasitic infestations and serum serology and stool testing.

7) Section 4.2.2 (Exclusion Criteria): Exclusion Criterion 16 was amended to confirm the diagnosis by stool sampling per local guidelines for subjects who have positive serology for *Ascaris Lumbricoides, Schistosoma Mansoni* or *Taenia Solium.* Due to the limited predictive value of serology assays, positive serologies must be confirmed by stool sampling. If the stool sampling is positive for *Schistosoma mansoni* or *Taenia solium* the subject will be excluded. If the serology is positive for *Ascaris lumbricoides,* the subjects will be treated with a single oral dose of 400mg albendazole. If albendazole is not licensed, the subject will be treated per local standard of care. Treatment with oral albendazole 400mg is almost 100% effective (Norhayati et al, 1997). All subjects will be treated with albendazole if tested positive for serology. The reason being that eggs do not appear in the stool for at least 40 days after infection; thus an early diagnosis, including during the phase of respiratory symptoms, cannot be made if the sole diagnostic marker is reliance upon eggs in feces. In addition, no eggs will be present in stool if the infection is due to male worms only.

8) Section 4.2.4.1(Rescreening of Subjects): Text was updated to allow for 2 re-screenings for patients who have screen failed for *Ascaris Lumbricoides, Schistosoma Mansoni or Taenia Solium*. Due to the limited predictive value of the diagnostic serology assays; subjects who tested positive for *Ascaris Lumbricoides, Schistosoma Mansoni or Taenia Solium* before may be rescreened.

9) Table 5.2-1 (Schedule of Study Procedures): Wording added to include stool sampling (if applicable).

10) Section 5.2.1.1 (Screening: Days -56 to -29): Wording added to include stool sampling (if applicable).

11) Section 5.3.2 (Clinical Laboratory Tests): Wording added to include stool sampling (if applicable).

Appendix 1 Definition of Anaphylaxis

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

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

AND AT LEAST ONE OF THE FOLLOWING

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

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

- Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).
- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
- Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).
- Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

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

Appendix 2 Symbicort® Patient Information

Investigative sites should be familiar with the dosing recommendations and safety profile of budesonide (Symbicort®). Information on the Symbicort® label, including updates to label changes, can be obtained from AstraZeneca via their mailing address or the Symbicort® websites.

International web site: http://www.symbicort.com

Appendix 3 Spiriva® Patient Information

Investigative sites should be familiar with the dosing recommendations and safety profile of Spiriva® HandiHaler®. Information on the Spiriva® HandiHaler® label, including updates to label changes, can be obtained from Boehringer Ingelheim via their mailing address or the Spiriva® website.

International web site: http://www.spiriva.com

Appendix 4 Bricanyl® Patient Information

Investigative sites should be familiar with the dosing recommendations and safety profile of Bricanyl® Turbuhaler®. Information on the Bricanyl® Turbuhaler® label, including updates to label changes, can be obtained from AstraZeneca.