AstraZeneca

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A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study to Evaluate the Onset of Effect and Time Course of Change in Lung Function with Benralizumab in Severe, Uncontrolled Asthma Patients with Eosinophilic Inflammation

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

VERSION HISTORY

Version 1.0, 07 July 2016
Initial creation

PROTOCOL SYNOPSIS

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study to Evaluate the Onset of Effect and Time Course of Change in Lung Function with Benralizumab in Severe, Uncontrolled Asthma Patients with Eosinophilic Inflammation

International Coordinating Investigator

[redacted]

Study site(s) and number of subjects planned

This study will be conducted worldwide in approximately 55 study centers. Target is to randomize 230 patients.

Study period		**Phase of development**
Estimated date of first subject enrolled	Q3 2016	Phase 3b
Estimated date of last subject completed	Q4 2017	

Study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate the onset of effect and the safety of a fixed 30 mg dose of benralizumab administered subcutaneously (SC) to patients with severe, uncontrolled asthma. Approximately 230 patients with peripheral blood eosinophil counts ≥300 cells/μL will be randomized globally to receive SC benralizumab 30 mg or placebo.

After enrolment, eligible patients will enter a 5-week screening/run-in period. Patients who meet eligibility criteria will enter a 12-week treatment period and receive 30 mg benralizumab or placebo at Day 0, Day 28 (±3 days), and Day 56 (±3 days). An End-of-Treatment (EOT) visit will be conducted at Day 84 (Week 12) and a follow-up (FU) visit will be conducted at Day 112 (Week 16).

Objectives

Primary objective	**Outcome measure**
To determine the effect of benralizumab on the time course of change (onset and maintenance of effect) on lung function	The average over the mean differences between benralizumab and placebo for the change from baseline (Visit 4) at Day 28 (Visit 8), Day 56 (Visit 9) and Day 84 (Visit 10) in pre-bronchodilator (BD) forced expiratory volume in 1 second ($FEV_{1)}$ will be used to determine if the study is positive and to determine maintenance of effect. The first post baseline timepoint where the p-value for the mean difference between benralizumab and placebo is less than or equal to 0.05 will be used to determine time to onset of effect.

Secondary objectives	**Outcome measure**
To determine time course of effect of benralizumab on blood eosinophils and correlate changes in eosinophil depletion with lung function	Change from baseline in blood eosinophils (from hematology) to end of treatment together with the correlation with lung function
To determine the effect of benralizumab on the time course of change and maintenance on lung function.	Change from baseline (Visit 4) in pre-BD FEV_1 at all clinic visits compared to placebo Change from baseline (Visit 4) in pre-BD forced vital capacity (FVC) at all clinic visits compared to placebo
To determine the time course of the effect of benralizumab on asthma control metrics	Change from baseline (Visit 4) in Asthma Control Quesitonnaire-6 (ACQ-6) score at all post-baseline assessment timepoints
To determine the time course of effect of benralizumab on health related quality of life	Change from baseline (Visit 4) in St. George's Respiratory Questionnaire (SGRQ) score at all post-baseline assessment timepoints

To determine the effect of benralizumab on the time course of change in exhaled nitric oxide (FeNO)	Change from baseline in FeNO (ppb) compared to placebo to end of treatment (Visit 10)

Safety objectives:	**Outcome measure**
To evaluate the pharmacokinetics (PK) and immunogenicity of benralizumab	• Serum PK • Anti-drug antibodies
To assess the safety and tolerability of benralizumab	• Adverse events (AEs) and serious adverse events (SAEs) • Laboratory variables • Physical Examination

Other objectives:	**Outcome measure**
To evaluate patient impression of overall asthma severity (PGI-S) and overall change from baseline as reported by the patient (PGI-C) and clinician (CGI-C)	• Change from baseline (Visit 4) in PGI-S at all post-baseline assessment timepoints • Clinician-reported global change in asthma from baseline (Visit 4) as measured by CGI-C • Patient-reported global change in asthma from baseline (Visit 4) as measured by PGI-C

Body plethysmography sub-study objectives

Sub-study primary objective	**Outcome Measure**
To determine the effect of benralizumab on the time course of change in lung function as assessed through body plethysmography	Change from baseline (Visit 4) to end of treatment (Visit 10) in the following measures compared to placebo: • Residual volume (RV)

Sub-study secondary objectives	**Outcome measure**
To determine the effect of benralizumab on the time course of change in lung function as assessed through body plethysmography	Change from baseline (Visit 4) to end of treatment (Visit 10) in the following measures compared to placebo : • Total lung capacity TLC) • RV/TLC ratio • Inspiratory capacity (IC) • Functional residual capacity (FRC) • Vital capacity (VC)
Sub-study other objectives	**Outcome measure**
To determine the effect of benralizumab on the time course of change in lung function as assessed through body plethysmography	Change from baseline (Visit 4) to end of treatment (Visit 10) in the following measures compared to placebo: • Specific airway resistance (SGaw) • Airway resistance (Raw)

Target subject population

Male and female patients 18 to 75 years of age with severe uncontrolled asthma will be enrolled.

Duration of treatment

After enrolment, eligible patients will enter a 5-week screening/run-in period. Patients who meet eligibility criteria will enter a 12-week treatment period and receive 30 mg benralizumab or placebo at Day 0, Day 28 (±3 days), and Day 56 (±3 days). An End-of-Treatment (EOT) visit will be conducted at Day 84 (Week 12) and a follow-up (FU) visit will be conducted at Day 112 (Week 16).

The total planned study duration for patient is a maximum of 22 weeks.

Investigational product, dosage and mode of administration

Benralizumab 30 mg/mL solution for injection in an accessorized pre-filled syringe (APFS) will be administered at the study center subcutaneously (SC) every 4 weeks for 3 doses (Day 0, Day 28 [±3 days], and Day 56 [±3days]).

Statistical methods

Approximately 230 subjects in total and 115 subjects in each treatment group are needed for this study based on the primary objective of the study to determine the effect of benralizumab on the time course of change (onset and maintenance of effect) of pre-bronchodilator (BD) FEV_1.

Subjects will be randomized in a 1:1 ratio to benralizumab or placebo. In order to have balanced number of subjects for region and the body plethysmography sub-study the randomization will be stratified for these variables.

The primary analysis method for primary endpoint, the change from baseline in pre-BD FEV_1 will be compared between benralizumab and placebo using a repeated measures analysis. Treatment group will be fitted as the explanatory variable; region, visit and treatment*visit interaction as fixed effects and baseline pre-bronchodilator FEV_1 as a covariate. The first post-baseline timepoint where the p-value for the mean difference between benralizumab and placebo is less than or equal to 0.05 will be used to determine time to onset of effect. The average over the mean differences between benralizumab and placebo based on the change from baseline (Visit 4, Day 0) to Days 28 (Visit 8), 56 (Visit 9) and 84 (Visit 10) in pre-BD FEV_1 will be used to determine if the study is positive as well as maintenance of effect. Contrasts will be used to obtain estimates of the treatment differences over Days 28, 56 and 84 as well as at each timepoint separately.

Efficacy analysis for the main study will be performed using the full analysis set, which consists of all randomized subjects who received at least 1 dose of investigational product.

Efficacy analyses for the body plethysmography sub-study will include the subset of patients who are randomized as part of the sub-study as described for the full analysis set.

All safety variables will be summarized descriptively. The safety analysis will be performed using the safety analysis set.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Table 1 List of abbreviations

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
Beta-hCG	Beta- human chorionic gonadotropin
BP	Blood pressure
BUN	Blood urea nitrogen
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CGI-C	Clinician Global Impression of Change
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of treatment
ePRO	Electronic patient reported outcome
EU	European Union
FeNO	Fractional exhaled Nitric Oxide
FEV_1	Forced expiratory volume in 1 second
FRC	Functional Residual Capacity
FSH	Follicle-stimulating hormone

Table 1 List of abbreviations

Abbreviation or special term	Explanation
FVC	Forced vital capacity
Gamma-GT	Gamma-glutamyl transpeptidase
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
GLI	The Global Lung Function Initiative
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
IC	Inspiratory Capacity
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
IL	Interleukin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-5Rα	Interleukin-5 receptor alpha subunit
ICI	International Coordinating Investigator
IM	Intramuscular
IP	Investigational product
IPD	Premature IP Discontinuation
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-acting β_2 agonists
LTRA	Leukotriene receptor antagonists
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralizing antibodies
OCS	Oral corticosteroids
PD	Pharmacodynamic(s)
PEF	Peak expiratory flow

Table 1 List of abbreviations

Abbreviation or special term	Explanation
PK	Pharmacokinetic(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PN	Predicted normal
Post-BD	Post-bronchodilator
Pre-BD	Pre-bronchodilator
PRO	Patient reported outcome
Raw	Airway resistance
RBC	Red blood cell
RV	Residual Volume
SABA	Short-acting β_2 agonists
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGaw	Specific Airway conductance
SGRQ	St. George's Respiratory Questionnaire
SUSARs	Suspected Unexpected Serious Adverse Reactions
TLC	Total Lung Capacity
ULN	Upper limit of normal
VC	Vital Capacity
WBC	White blood cell
WBDC	Web-based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Asthma is a syndrome characterized by airway inflammation, reversible airway obstruction, and airway hyperresponsiveness. Patients present clinically with recurrent wheezing, shortness of breath, cough, and chest tightness. Asthma is a leading cause of morbidity with a global prevalence of approximately 300 million; it is estimated that the number of people with asthma may increase to 400-450 million people worldwide by 2025 (Masoli et al 2004).

The current approach to anti-inflammatory controller therapy in asthma is based on a stepwise intensification of a daily maintenance regimen centered around inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA), with the addition of long-acting β2 agonists (LABA) in patients with more severe asthma (GINA 2016, NAEPP 2007). Despite treatment per management guidelines, up to 50% of patients have asthma that is not well controlled (ATS 2005; Bateman et al 2010). This results in considerable impact on quality of life, disproportionate use of healthcare resources, and adverse reactions from regular systemic steroid use. Therefore, there remains an unmet medical need for patients whose asthma is not controlled by existing therapies.

The observed variability in clinical response to currently available asthma therapies appears to be related, in part, to distinctive inflammatory phenotypes (Wenzel 2012). In particular, asthma associated with eosinophilic inflammation in the airway (often referred to as eosinophilic asthma) is common (approximately 40% to 60% of asthmatics) with the degree of eosinophilia associated with clinical severity including the risk of asthma exacerbations (Bousquet et al 1990, Louis et al 2000, Di Franco et al 2003, Scott and Wardlaw 2006, Saito et al 2015, Simpson et al 2006). Interleukin-5 (IL-5) is a key cytokine essential for eosinophil trafficking and survival (Molfino et al 2011). Clinical trials of the anti-IL-5 antibodies mepolizumab and reslizumab in patients with uncontrolled eosinophilic asthma have shown benefit in reducing asthma exacerbation, improving lung function, and reducing symptoms (Castro et al 2011, Ortega et al 2014). These promising results support continued development of therapies targeting eosinophils in eosinophilic asthmatics.

Benralizumab (MEDI-563) is a humanized, afucosylated, monoclonal antibody that binds specifically to the human IL-5 receptor alpha subunit (IL-5Rα) on the target cell. The IL-5 receptor (IL-5R) is expressed almost exclusively on the surface of eosinophils and basophils (Takatsu et al 1994, Toba et al 1999). Afucosylation confers enhanced antibody-dependent cellular cytotoxicity (ADCC) which results in highly efficient eosinophil depletion by apoptosis (Kolbeck et al 2010). Single and repeated doses of benralizumab in mild to severe asthma patients has resulted in depletion of blood and airway eosinophils (Busse et al 2010, Molfino et al 2012, Laviolette et al 2013). Also, a recent dose-finding trial in severe asthma proved benralizumab to have benefit across a range of asthma outcomes including reductions in asthma exacerbations, improvements in lung function, and reduction in symptoms (Castro et al 2014).

Benralizumab is currently being studied in Phase 3 in severe asthmatics with a history of exacerbations, still symptomatic despite using medium-to-high dose ICS/LABAs with or without oral corticosteroids or additional controller medications. The dose being studied for these trials is 30 mg, a dose derived from pharmacokinetic/pharmacodynamic (PK/PD) modeling of the Phase 2 dose finding study, administered in 2 dosing regimens – either 30 mg every 4 weeks (Q4W) or 30 mg every 4 weeks (Q4W) for the first 3 doses followed by dosing every 8 weeks (Q8W) thereafterThe primary endpoint in each study is the annual rate of asthma-related exacerbations with key secondary endpoints being FEV_1 and asthma symptoms as defined by a daily patient diary.

The effect of benralizumab on depletion of blood eosinophils is rapid, with time to maximum effect on depletion of eosinophils in blood (ie, below level of detection) within 24 hours in asthmatic subjects (Laviolette et al 2013; Busse et al 2010) and within 6 hours in healthy subjects (Saito et al 2015). Benralizumab also depletes eosinophils in lung tissue and sputum in mild to moderate asthmatics (Laviolette et al 2013) where benralizumab showed a median 61% reduction in lung tissue eosinophils at 28 days post dosing (at 1 mg/kg i.v.) and a median 96% reduction at 84 days post dosing (combined 100 mg and 200 mg s.c.). This study is designed to characterize the time of onset of changes in lung function relative to the depletion of eosinophils in the peripheral blood.

1.2 Rationale for study design, doses and control groups

This is a randomized, double blind, placebo controlled global study designed to investigate the onset of effect of benralizumab (30 mg) administered subcutaneously (SC) on lung function in severe asthmatics still uncontrolled on standard of care therapy(-ies). Three doses will be given every 4 weeks on Day 0, Day 28 (±3 days) and Day 56 (±3 days).

The dose chosen, 30 mg SC, is based on all available efficacy and safety data, as well as population exposure-response modelling and stochastic simulations from earlier benralizumab trials.

A 12 week treatment duration, with 3 doses of benralizumab given every 4 weeks, will characterize the full time course of effect of benralizumab on lung function profiling the effect on FEV_1 from onset to the estimated plateau of effect at 12 weeks, as observed in the Ph2b study.

1.3 Rationale for the sub-study design, doses and control groups

For the sub-study, the primary efficacy variable is the change from baseline in Residual volume (RV) as assessed through body plethysmography up until the EOT at Visit 10. Secondary variables will characterize a change from baseline until V10 in lung volume subdivisions which include total lung capacity (TLC), RV/TLC ratio, inspiratory capacity (IC), functional residual capacity (FRC), and vital capacity (VC).

Other variables will characterize a change in airway resistance (Raw) and specific airway resistance (SGaw)

Previous studies have shown an improvement in FEV_1, the substudy will evaluate the effect of benralizumab on the different lung subdivisions.

1.4 Benefit/risk and ethical assessment

Benralizumab is being studied in severe asthma where there are few treatment options for patients whose asthma remains uncontrolled on high dose ICS/LABA and oral corticosteroids (GINA 2016). In adult patients whose asthma was poorly controlled on medium-to-high dose ICS/LABA therapy, benralizumab at doses of ≥20 mg produced improvements in multiple

metrics of asthma control including the annual rate of asthma exacerbations, lung function, ACQ-6 scores, and symptoms (Castro et al 2014).

Development of anti-drug antibodies (ADA) to benralizumab has been documented. Theoretical risks of developing ADA include decreased drug efficacy and hypersensitivity reactions (eg, anaphylaxis or immune complex disease). Eosinophils are a prominent feature of the inflammatory response to helminthic parasitic infections and the presence of infiltrating eosinophils has been circumstantially associated with a positive prognosis in certain solid tumors. Therefore, there is a theoretical risk that prolonged eosinophil depletion may diminish the ability to defend against helminthic parasites, or negatively impact the natural history of certain malignant tumors. Risk minimization measures herein include exclusion of patients with untreated parasitic infection and active or recent malignancy, in conjunction with the performance of routine pharmacovigilance activities.

The efficacy and safety data obtained to date support the continued clinical development of benralizumab in patients with asthma.

A detailed assessment of the overall risk/benefit of benralizumab is given in the Investigator's Brochure.

1.5 Study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate the onset of effect and the safety of a fixed 30 mg dose of benralizumab administered subcutaneously (SC) to patients with severe, uncontrolled asthma. Approximately 230 patients with peripheral blood eosinophil counts ≥300 cells/μL will be randomized globally to receive SC benralizumab 30 mg or placebo.

After enrolment, eligible patients will enter a 5-week screening/run-in period. Patients who meet eligibility criteria will enter a 12-week treatment period and receive 30 mg benralizumab or placebo at Day 0, Day 28 (±3 days), and Day 56 (±3 days). An End-of-Treatment (EOT) visit will be conducted at Day 84 (Week 12) and a follow-up (FU) visit will be conducted at Day 112 (Week 16).

Figure 1 Main study flow chart

Enrollment	Run-in period		Treatment period							Follow-up period
Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**
Day -35	Day -21	Day -7	Day 0	Day 3	Day 7	Day 14	Day 28	Day 56	Day 84	Day 112
±0 d	±2 d	±2 d	±0 d	±1 d	±1 d	±3 d	±3 d	±3 d	±7 d	±7 d
Post BD Only[a]	Post BD[a]	Post BD[a]	-	-	-	-	-	-	-	-
-	Pre-BD FEV_1[b]	Pre-BD FEV_1[b]	Pre-BD FEV_1	Pre-BD FEV_1	Pre-BD FEV_1	Pre-BD FEV_1	Pre-BD FEV_1	Pre-BD FEV_1	Pre-BD FEV_1	Pre-BD FEV_1
-	-	-	**Dose 1**	-	-	-	**Dose 2**	**Dose 3**	-	-

[a] In case patient meets maintenance medication restrictions for the respiratory testing at Visit 1, only reversibility testing can be performed at Visit 1. If a patient fails the protocol-specified reversibility criterion (≥ 12% and 200 ml) at Visit 1, a second attempt is allowed at Visit 2 or Visit 3.

[b] Pre BD FEV1 spirometry should be recorded at Visit 2 as well as at Visit 3, irrespective of whether the patient has met protocol specified pre-bronchodilator FEV1 criterion (<80%) at Visit 2 or not. The Pre BD FEV1 criteria must be met at either Visit 2 or at Visit 3.

d days; FEV1 Forced Expiratory Volume in 1 sec measurement (spirometry); pre-BD pre-bronchodilator; post-BD post bronchodilator.

Figure 2 Body plethysmography sub-study flow chart

Enrollment	Run-in period		Treatment period							Follow-up period
Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**
Day -35	Day -21	Day -7	Day 0	Day 3	Day 7	Day 14	Day 28	Day 56	Day 84	Day 112
±0 d	±2 d	±2 d	±0 d	±1 d	±1 d	±3 d	±3 d	±3 d	±7 d	±7 d
Post BD Only[a]	Post BD[a]	-	-	-	-	-	-	-	-	-
-	Pre-BD FEV_1[b]	Pre-BD FEV_1[b]	Pre-BD FEV_1	Pre-BD FEV_1	Pre-BD FEV_1	Pre-BD FEV_1	Pre-BD FEV_1	Pre-BD FEV_1	Pre-BD FEV_1	Pre-BD FEV_1
-	-	BB	BB	-	BB	BB	BB	BB	BB	-
-	-	-	**Dose 1**	-	-	-	**Dose 2**	**Dose 3**	-	-

[a] In case patient meets maintenance medication restrictions for the respiratory testing at Visit 1, only reversibility testing can be performed at Visit 1. If a patient fails the protocol-specified reversibility criterion (≥ 12% and 200 ml) at Visit 1, a second attempt is allowed only at Visit 2

[b] Pre BD FEV1 spirometry should be done at Visit 2. If a patient fails the protocol-specified pre-bronchodilator FEV1 criterion (<80%) at Visit 2, a second attempt is allowed at Visit 3 for patients in main study as well as the sub-study. For the patients participating in the body plethysmography sub study a second attempt is allowed only at Visit 2.

BB Body Box for whole body plethysmography; d days; FEV1 Forced Expiratory Volume in 1 sec measurement (spirometry); pre-BD pre-bronchodilator; post-BD post bronchodilator.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary objective:	**Outcome measure:**
To determine the effect of benralizumab on the time course of change (onset and maintenance of effect) on lung function	The average over the mean differences between benralizumab and placebo for the change from baseline (Visit 4) at Day 28 (Visit 8), Day 56 (Visit 9) and Day 84 (Visit 10) in pre-BD FEV1 will be used to determine if the study is positive and to determine maintenance of effect. The first post baseline timepoint where the p-value for the mean difference between benralizumab and placebo is less than or equal to 0.05 will be used to determine time to onset of effect.

2.2 Secondary objectives

Secondary objectives	**Outcome measure**
To determine time course of effect of benralizumab on blood eosinophils and correlate changes in eosinophil depletion with lung function	Change from baseline in blood eosinophils (from hematology) to end of treatment together with the correlation with lung function
To determine the effect of benralizumab on the time course of change and maintenance on lung function.	Change from baseline (Visit 4) in pre-BD FEV_1 at all clinic visits compared to placebo Change from baseline (Visit 4) in pre-BD forced vital capacity (FVC) at all clinic visits compared to placebo
To determine the time course of the effect of benralizumab on asthma control metrics	Change from baseline (Visit 4) in Asthma Control Quesitonnaire-6 (ACQ-6) score at all post-baseline assessment timepoints
To determine the time course of effect of benralizumab on health related quality of life	Change from baseline (Visit 4) in St. George's Respiratory Questionnaire (SGRQ) score at all post-baseline assessment timepoints
To determine the effect of benralizumab on the time course of change in exhaled nitric oxide (FeNO)	Change from baseline in FeNO (ppb) compared to placebo to end of treatment (Visit 10)

2.3 Safety objectives

Safety objectives:	**Outcome measure**
To evaluate the pharmacokinetics (PK) and immunogenicity of benralizumab	• Serum PK • Anti-drug antibodies
To assess the safety and tolerability of benralizumab	• Adverse events (AEs) and serious adverse events (SAEs) • Laboratory variables • Physical Examination

2.4 Other objectives for the main study

Other objectives:	**Outcome measure**
To evaluate patient impression of overall asthma severity (PGI-S) and overall change from baseline as reported by the patient (PGI-C) and clinician (CGI-C)	• Change from baseline (Visit 4) in PGI-S at all post-baseline assessment timepoints • Clinician-reported global change in asthma from baseline (Visit 4) as measured by CGI-C • Patient-reported global change in asthma from baseline (Visit 4) as measured by PGI-C

2.5 Body plethysmography sub-study primary objectives

Sub-study primary objective	**Outcome measure**
To determine the effect of benralizumab on the time course of change in lung function as assessed through body plethysmography	Change from baseline (Visit 4) to end of treatment (Visit 10) in the following measures compared to placebo: • Residual volume (RV)

2.6 Body plethysmography sub-study secondary objectives

Sub-study secondary objectives	Outcome measure
To determine the effect of benralizumab on the time course of change in lung function as assessed through body plethysmography	Change from baseline (Visit 4) to end of treatment (Visit 10) in the following measures compared to placebo : • Total lung capacity TLC) • RV/TLC ratio • Inspiratory capacity (IC) • Functional residual capacity (FRC) • Vital capacity (VC)

2.7 Body plethysmography sub-study other objectives

Sub-study other objectives	Outcome measure
To determine the effect of benralizumab on the time course of change in lung function as assessed through body plethysmography	Change from baseline (Visit 4) to end of treatment (Visit 10) in the following measures compared to placebo: • Specific airway resistance (SGaw) • Airway resistance (Raw)

3. SUBJECT SELECTION, ENROLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study subjects should meet the following criteria:

1. Written informed consent for study participation must be obtained prior to any study related procedures being performed and according to international guidelines and/or applicable European Union (EU) guidelines.

2. Female and male aged 18 to 75 years inclusively at the time of Visit 1

3. Documented current treatment with ICS and LABA for at least 30 days prior to Visit 1.

- For ICS/LABA combination preparations, high-strength maintenance doses approved in the given country will meet this criterion.

- If the ICS and LABA therapies are given by separate inhalers, the ICS dose must be >500 µg fluticasone propionate dry powder formulation or equivalent daily (see Appendix F).

- Additional asthma controller medications, eg, oral corticosteroids, long-acting anti-muscarinics (LAMAs), LTRAs, theophylline etc. are allowed if they have been used for at least 30 days prior to Visit 1.

4. History of at least 2 asthma exacerbations that required treatment with systemic corticosteroids (intramuscular (IM), intravenous (IV), or oral) in the 12 months prior to Visit 1. For patients receiving corticosteroids as a maintenance therapy, the corticosteroid treatment for the exacerbation is defined as a temporary increase of their maintenance dose.

5. Pre-bronchodilator (pre-BD) FEV_1 of < 80% predicted at Visit 2 or Visit 3

6. ACQ-6 score ≥1.5 at Visit 1

7. Evidence of asthma as documented by airway reversibility (FEV_1 ≥12% and 200 ml) demonstrated at Visit 1, Visit 2 or Visit 3 (as described in Section 5.1.1.1). For patients entering the body plethysmography sub-study, reversibility must be demonstrated at Visit 1 or at Visit 2 only.

8. Peripheral blood eosinophil count of ≥300 cells/µL assessed by central lab at Visit 1

9. Women of childbearing potential (WOCBP) must use an effective form of birth control (confirmed by the Investigator), eg, true sexual abstinence, a vasectomized sexual partner, Implanon®, female sterilization by tubal occlusion, any effective IUD Intrauterine device/IUS Ievonorgestrel Intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch ™ or Nuvaring™. WOCBP must agree to use birth control, as defined above, from enrolment, throughout the study duration and until 16 weeks after last dose of investigational product (IP). WOCBP must also have negative serum pregnancy test result on Visit 1.

   Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years old are considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels in the postmenopausal range.

- Women ≥50 years old are considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.

10. All male patients who are sexually active must agree to use a double barrier method of contraception (condom with spermicide) from the first dose of IP until 16 weeks after their last dose.

11. Weight of ≥40 kg

3.1.1 Additional inclusion criteria applicable for the Body Plethysmography sub-study

1. Residual volume ≥125% of predicted at Visit 3.

   Patients who do not meet this criterion and/or are not able to take body plethysmography assessments, should continue in the main study only.

3.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Clinically important pulmonary disease other than asthma (eg, active lung infection, COPD, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome)

2. Life-threatening asthma defined as episodes requiring intubation associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma related syncopal episodes within the 12 months prior to Visit 1.

3. Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the screening/run-in period

4. An upper respiratory tract infection or an asthma exacerbation that required treatment with systemic corticosteroids or an increase in regular maintenance dose of OCS during the screening/run-in period prior to randomization Visit 4

5. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:

- Affect the safety of the patient throughout the study

- Influence the findings of the studies or their interpretations
- Impede the patient's ability to complete the entire duration of study

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

7. History of anaphylaxis to any biologic therapy

8. History of Guillain-Barré syndrome

9. A helminth parasitic infection diagnosed within 24 weeks prior to the date informed consent is obtained that has not been treated with, or has failed to respond to standard of care therapy

10. Any clinically significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry, or urinalysis during screening period, which in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to complete entire duration of the study

11. Any clinically significant cardiac disease or any electrocardiogram (ECG) abnormality obtained during the screening/run-in period, which in the opinion of the Investigator may put the patient at risk or interfere with study assessments

12. History of alcohol or drug abuse within 12 months prior to the date informed consent is obtained

13. Positive hepatitis B surface antigen, or hepatitis C virus antibody serology, or a positive medical history for hepatitis B or C. Patients with a history of hepatitis B vaccination without history of hepatitis B are allowed to enroll

14. A history of known immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test

15. Current smokers or former smokers with a smoking history of ≥10 pack years. A former smoker is defined as a patient who quit smoking at least 6 months prior to Visit 1.

16. Current malignancy, or history of malignancy, except for:

- Patients who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained.

- Patients who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained.

17. Use of immunosuppressive medication (including but not limited to: oral corticosteroids [for reasons other than asthma], methotrexate, troleandomycin, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroids or any experimental anti-inflammatory therapy) within 3 months prior to the date informed consent

18. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥1.5 times the upper limit of normal (ULN) confirmed during screening period.

19. Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent is obtained

20. Receipt of any marketed (eg, omalizumab, mepolizumab etc.) or investigational biologic within 4 months or 5 half-lives prior to the date informed consent is obtained, whichever is longer

21. Receipt of live attenuated vaccines 30 days prior to the date of randomization.

22. Receipt of any investigational medication within 30 days or 5 half-lives prior to randomization, whichever is longer

23. Previously received benralizumab (MEDI-563)

24. Planned surgical procedures during the conduct of the study

25. Currently breastfeeding or lactating women

26. Previous randomization in the present study

27. Concurrent enrolment in another interventional or post-authorization safety study (PASS).

28. AstraZeneca staff involved in the planning and/or conduct of the study

29. Employees of the study center or any other individuals involved with the conduct of the study or immediate family members of such individuals

3.3 Eligibility criteria to be confirmed at randomization Visit 4.

3.3.1 Inclusion criteria at randomization Visit 4

1. At least 1 of the following within 7 days prior to randomization:

   – Daytime or nighttime asthma symptoms for 2 or more days;

- Rescue SABA use for 2 or more days;
- Nighttime awakenings due to asthma at least 1 night during the 7-day period

2. ACQ >0.75 at Visit 4 prior to randomization.

3. A negative urine pregnancy test in WOCBP prior to administration of IP

3.3.2 Exclusion criteria at randomization Visit 4

1. Greater than/equal to 20% change in mean Pre BD FEV1 value (mean of the Pre BD FEV1 taken 30 min (+/- 10 min) and 60 min (+/- 10 min) prior to dosing) at randomization Visit 4 (Day 0) from the mean pre BD FEV1 calculated from the pre BD FEV1 recorded at Visit 2 and Visit 3.

Procedures for withdrawal of incorrectly enrolled subjects see Section 3.5.

3.4 Subject enrolment and randomization

Investigator(s) should keep a record of all subjects who entered study screening (subject screening log).

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject before any study specific procedures are performed.

2. Assign potential subject a unique enrolment number, beginning with 'E#' via interactive web/voice response system (IWRS/IVRS).

3. Determine subject eligibility. See Section 2.7–Section 3.3.

4. Assign eligible subject a unique randomization code via IWRS/IVRS

If a subject withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused.

Patients will be allocated to treatment arms in a 1:1 ratio. Specific information concerning the use of the IWRS/IVRS will be provided in the separate manual. Randomized patients who discontinue from the investigational product administration will not be replaced.

3.5 Procedures for handling incorrectly enrolled or randomized subjects

Patients who fail to meet the eligibility criteria should not, under any circumstance, be randomized or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca Study Physician must ensure all decisions are appropriately documented.

3.6 Methods for assigning treatment groups

Patients will be stratified by geographical region and also by whether patients enter the whole body plethysmography sub-study. Randomization codes will be assigned strictly sequentially in each stratum as patients become eligible for randomization.

3.7 Methods for ensuring blinding

The study will be conducted in double-blind fashion. AstraZeneca staff involved in the study, the patients, and the Investigators involved in the treatment of the patients or in their clinical evaluation will not be aware of the treatment allocation.

Placebo solution will be visually matched with benralizumab solution. Both benralizumab and placebo will be provided in an accessorized pre-filled syringe (APFS).

3.7.1 Maintaining the blind to the patient's blood eosinophils counts

While not entirely specific, patients on active benralizumab treatment are expected to have lower blood eosinophil counts than patients on placebo. In order to mitigate potential unblinding on this basis, per protocol hematology will be run by the central laboratory. From Visit 4 on, eosinophil, basophil and monocyte counts will be redacted from any central laboratory reports sent to investigative sites to prevent the Principal Investigator/designee from possibly deducing the 'eosinophil + basophil' contribution to the complete blood count.

3.8 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomization.
The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

3.9 Restrictions

3.9.1 Asthma medication restrictions

(a) **Use of SABA**

Regularly scheduled or prophylactic SABA use is discouraged from enrolment and throughout the study duration.

(b) **Use of short-acting anticholinergics** (eg, ipratropium) as a rescue treatment for worsening asthma symptoms is not allowed from enrolment and throughout the study duration.

(c) **Use of long-acting beta-agonists** as a reliever (eg, Symbicort Maintenance And Reliever Treatment) is not allowed from enrolment and throughout the study duration.

(d) **Maintenance of asthma controller medications**

Changes to the patient's background medications are not allowed during the study.

Asthma exacerbations should be treated with oral or other systemic corticosteroids according to standard practice.

(e) **Asthma medication restrictions on the days of scheduled lung function assessment visit**

Lung function assessments include FeNO, spirometry and whole body plethysmography (for a subset of patients). Procedures will be performed at the study center per the study plan and procedures in the following order: FeNO, spirometry, body plethysmography (if applicable). Restrictions to the patient's background medication prior to the assessments are described below.

Patients should withhold their usual maintenance therapies on the day(s) when lung function testing is being performed.

SABAs should be withheld for 6 or more hours before spirometry. Twice daily LABA- or LAMA-containing therapies should be withheld for 12-24 hours and once daily LABA- or LAMA-containing therapies for >24 hours before spirometry. LTRA should be restricted for >24 hours and twice daily theophyllines should be withheld for at least 12- 24 hours and once daily for >24 hours before spirometry assessments.

If the patient has taken rescue SABA within 6 hours of the planned center visit spirometry, they should remain at the center until the 6 hour withholding time has been reached (as long as that does not exceed the 1.5 hour spirometry window). On

Visits 1, 2, 3 and visits 5 to Visit 11 they can return on another day within the visit window.

3.9.1.1 Other medication restrictions

(a) Use of immunosuppressive medications is not allowed. Topical administration of immunosuppressive medication may be allowed at the discretion of the Investigator. Refer to section 3.2 and exclusion criterion 17 for examples and further details.

(b) Receipt of live attenuated vaccines within 30 days prior to randomization, during the treatment period, and for 16 weeks (5 half-lives) after the last dose of the IP is not allowed

A table with medication-related restrictions is presented in Appendix E.

3.9.1.2 Other restrictions

(a) Fertile and sexually active patients or their partners should use effective contraceptive methods throughout the study and at least for 16 weeks (5 half-lives) after last administration of the IP. Male patients should refrain from fathering child or donating sperm from the time of informed consent, and for 16 weeks (5 half-lives) after last dose of IP (see Inclusion criterion 10)

(b) Patients must abstain from donating blood and plasma from the time of informed consent, and for 16 weeks (5 half-lives) after last dose of IP.

(c) Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the center.

(d) Patients should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the center.

3.10 Discontinuation of investigational product

Subjects may be discontinued from investigational product (IP) in the following situations:

(a) Patient decision. The patient is free to discontinue treatment at any time, without prejudice to further treatment (see Section 3.10.1)

(b) Adverse event (AE) that in the opinion of the Investigator contraindicates further dosing

(c) Risk to patient as judged by the Investigator or AstraZeneca

(d) Pregnancy

(e) Lost to follow-up[1]

(f) Severe non-compliance to the study protocol

(g) Development of any study specific criteria for discontinuation

- Anaphylactic reaction to the investigational product requiring administration of epinephrine
- Development of helminth parasitic infestations requiring hospitalization
- An asthma-related event requiring mechanical ventilation

3.10.1 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue investigational product or withdraw from the study (ie, investigational product and assessments – see Section 3.11), without prejudice to further treatment. A subject that decides to discontinue investigational should always be asked about the reason(s) and the presence of any adverse events.

All patients must be administered the first dose of IP. If the patient misses the first IP administration they must be discontinued from the study and should return for IPD visit. If the patient receives the first IP administration but misses both the 2nd and the 3rd dose they must be discontinued from the study and should return for the IPD visit. If the patient receives the first IP administration but misses either the 2nd or 3rd dose they need not discontinue from the study

All patients who prematurely discontinue investigational product should return to the study center and complete the procedures described for the premature IP Discontinuation (IPD) visit within 4 weeks ±3 days after the last dose of IP. At that visit, although no longer on IP, patients should be encouraged to remain in the study to complete all subsequent study visits, procedures, and assessments. Note that in this case, the IPD visit replaces the nearest regular visit while the following visits continue as possible

If the patient is not willing to participate further in the study after the IPD visit, the patient should still return for a follow up visit 8 weeks ±3 days after the last dose of IP for final study-related assessments.

The reasons for premature discontinuation of IP should be recorded in the eCRF.

[1] 'Patient is considered lost to follow up when any of the following attempts of contact are failed: 3 attempts of either phone calls, faxes or emails; having sent 1 registered letter/certified mail; or 1 unsuccessful effort to check the vital status of the patient using publicly available sources, if allowed by local regulations.

If a subject is withdrawn from study, see Section 3.11.

3.11 Criteria for withdrawal

3.11.1 Screen failures

Screen failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

3.11.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study.

If a subject withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

3.12 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 2 Study plan - Run-in period; Visit 1 to Visit 3

Assessment/Activity	Refer to	Enrolment	Run-in	
		Visit 1	Visit 2	Visit 3
		D -35	D -21 (+/-2 days)	D -7 (+/- 2 days)
General procedures:				
Informed consent	10.4	X		
Inclusion/exclusion criteria	3.1/3.2	X	X	X
Demographics	4.1.1	X		
Medical and asthma history	4.1.1	X		
Patient Reported Outcome assessments:				
ACQ-6	5.3.2.1	X[c]		
Safety assessments:				
Complete physical examination	5.2.2.1/5.2.2.2	X		
Vital signs	5.2.4		X	X
Weight, height, BMI	5.3.1	X		
ECG	5.2.3.1	X		
Adverse events	6	X	X	X
Concomitant medication	7.7/3.9.1/3.9.1.1	X	X	X
Laboratory assessments:				
Clinical chemistry	5.2.1	X		
Hematology	5.2.1	X		
Urinanalysis	5.2.1	X		
Serum pregnancy test	5.2.1.1	X		
Serology (Hepatitis B, C, HIV-1, HIV-2)	5.3.3.1	X		
FSH	5.2.1.1	X[b]		
Lung function assessments:				

Table 2 Study plan - Run-in period; Visit 1 to Visit 3

Assessment/Activity	Refer to	Enrolment	Run-in	
		Visit 1	Visit 2	Visit 3
		D -35	D -21 (+/-2 days)	D -7 (+/- 2 days)
Exhaled NO (FeNO)	5.1.2		X	
Spirometry (Pre-BD FEV_1)	5.1.1		X[d]	X[d]
Reversibility (post-BD FEV_1)	5.1.1.1	X[e,f]	X[e,f]	X[e]
Sub-study assessments (if applicable):				
Whole body plethysmography	5.4.1			X

a This analysis will be only applicable for WOCBP patients.
b FSH test done only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for >=12 months
c All patients must meet ACQ6 ≥1.5 at Visit 1. If this criteria is not met the patient must be screen failed and will not be allowed to rescreen.
d For patients in the main study and the sub-study: The Pre BD FEV_1 must be conducted at Visit 2 and at Visit 3. The Pre-BD FEV_1 criteria must be met at either Visit 2 or at Visit 3.
e For patients in the main study: If the patient did not meet Reversibility criteria at Visit 1, further attempts may be conducted at Visit 2 and at Visit 3. Reversibility testing must be performed using the algorithm as detailed in section 5.1.1.1.
f For patients in the Body plethysmography sub-study: If the patient did not meet the reversibility criteria (using the algorithm as per section 5.1.1.1) at Visit 1, a further attempt may be conducted at Visit 2 only.

ACQ-6 Asthma Control Questionnaire 6; BMI Body Mass Index; FeNO Fractional exhaled Nitric Oxide; FEV1 Forced expiratory volume in 1 sec; FSH Follicle-stimulating hormone; HIV Human Immunodeficiency virus; pre-BD pre-bronchodilator; post-BD post-bronchodilator; D Day; ECG Electrocardiogram; NO nitric oxide; V Visit; W Week; WOCBP Women of childbearing potential

Table 3 Study Plan - Randomization, treatment period, follow-up; Visit 4 to Visit 11

Assessment/ activity	Refer to	Treatment						EOT	IPD	FU	Uns[b]
		V4 (D0)	V5 (D3)	V6 (D7)	V7 (D14)	V8 (D28)	V9 (D56)	V10 (D84)		V11 (D112)	
		Visit window (days)[a)]									
			+1	±1	±3	±3	±3	±7	±7	±7	N/A
General procedures:											
Inclusion/ exclusion criteria	3.1/3.2/ 3.3.1/ 3.3.2	X									
Randomization	4.2/3.6	X									
Patient and clinician Reported Outcome assessments:											
ACQ-6	5.3.2.1	X[g]			X	X	X	X	X		
SGRQ	5.3.2.2	X				X	X	X	X		
PGI-S	5.3.2.3	X		X	X	X	X	X	X		
PGI-C	5.3.2.4			X	X	X	X	X	X		
CGI-C	5.3.2.4		X	X	X	X	X	X	X		
Safety assessments:											
Complete physical examination	5.2.2.1	X						X	X		
Brief physical examination	5.2.2.2			X		X	X			X	X[b]

Table 3 Study Plan - Randomization, treatment period, follow-up; Visit 4 to Visit 11

Assessment/ activity	Refer to	Treatment						EOT	IPD	FU	Uns[b]
		V4 (D0)	V5 (D3)	V6 (D7)	V7 (D14)	V8 (D28)	V9 (D56)	V10 (D84)		V11 (D112)	
		Visit window (days)[a]									
			+1	±1	±3	±3	±3	±7	±7	±7	N/A
ECG	5.2.3.1									X	
Vital signs	5.2.4	X	X	X	X	X	X	X	X	X	X[b]
Adverse events	6	X	X	X	X	X	X	X	X	X	X[b]
Concomitant medication	7.7/3.9.1 /3.9.1.1	X	X	X	X	X	X	X	X	X	X[b]
Laboratory assessments:											
Clinical chemistry	5.2.1	X						X	X	X	
Hematology	5.2.1	X						X	X	X	
Blood for eosinophil count[c]	5.2.1/ 3.7.1	X	X	X	X	X	X	X	X	X	
Total IgE	5.3.3.2	X									
Serum pregnancy[d]	5.2.1.1							X	X	X	
Urinanalysis	5.2.1							X	X		
Urine pregnancy test, dipstick	5.2.1.1	X				X	X	X	X	X	
PK[e]	5.3.4	X	X	X	X	X	X	X	X		
ADA/nAb[f]	5.3.5.3	X						X	X		

Table 3 Study Plan - Randomization, treatment period, follow-up; Visit 4 to Visit 11

Assessment/ activity	Refer to	Treatment						EOT	IPD	FU	Uns[b]
		V4 (D0)	V5 (D3)	V6 (D7)	V7 (D14)	V8 (D28)	V9 (D56)	V10 (D84)		V11 (D112)	
		Visit window (days)[a]									
			+1	±1	±3	±3	±3	±7	±7	±7	N/A
Lung function assessments:											
Spirometry (pre-BD FEV_1)	5.1.1	X[h]	X	X	X	X	X	X	X	X	
Exhaled NO (FeNO)	5.1.2	X	X	X	X	X	X	X	X		
Sub-study assessments: (if applicable)											
Whole body plethysmography	5.4.1	X		X	X	X	X	X	X		
Randomization:											
Randomization	4.3/3.6	X									
Investigational Product administration											
Benralizumab/ placebo	7.2/7.5/ 7.6	X				X	X				

a All visits are to be scheduled from the date of randomization, not from the date of previous visit, except for early discontinuation from IP (see Section 3.10 for details)

b Unscheduled visits may be initiated as needed, and any additional assessments may performed at these visits, at the discretion of the Investigator. Procedures listed in the table are mandatory for each UNS visit.

c Blood eosinophil count will assessed in central laboratory as a part of the hematology panel but eosinophil, basophil and monocyte count will be redacted from the reports available for investigative sites

d This analysis will be only applicable for WOCBP patients.

e On dosing visits PK will be collected pre-dose
f Neutralizing antibody (nAb) testing will occur for all samples that are ADA positive. Samples that are ADA negative will not be tested for nAb.
g The patient must have an ACQ 6 >0.75 prior to randomization. If not the patient must be screen failed and cannot be rescreened
h Pre-BD FEV1 must be conducted 60 min (+/- 10 min) and 30 min (+/- 10 min) prior to randomization and assessed against exclusion criteria in section 3.3.2.

ACQ-6 Asthma Control Questionnaire 6; ADA anti-drug antibodies; CGI-C Clinician Global Impression of Change; D Day; ECG Electrocardiogram; FeNO Fractional exhaled Nitric Oxide; FEV1 Forced expiratory volume in 1 sec; IgE Immunoglobulin E; IPD Premature Investigational Product Discontinuation; nAb Neutralizing antibodies; NO nitric oxide; PK Pharmacokinetics; PGI-C Patient Global Impression of Change; PGI-S Patient Global Impression of Severity; pre-BD pre-bronchodilator; post-BD post-bronchodilator; SGRQ St. George's Respiratory Questionnaire; UNS Unscheduled visit; V Visit; W Week; WOCBP Women of childbearing potential

4.1 Enrolment/screening period

4.1.1 Enrolment (Visit 1) Day -35

Each potential patient will provide written informed consent prior to any study specific procedures and undergo assessments applicable for the visit (see Table 2).

Demographics data collected will include date of birth/age, sex, race and ethnicity.

Patient must sign the Informed Consent Form (ICF) prior to any Visit 1 procedures and prior being instructed to withhold any medication. Registration of patient's enrolment via IWRS/IVRS should occur on the day of ICF signature.

Visit 1 assessments are primarily concerned with confirmation of the asthma disease state and the requisite level of severity based on background medications.

A record of physician-diagnosed asthma is required in source documentation prior to enrolment. A patient's verbal history suggestive of asthma symptoms, but without supporting documentation, is not sufficient to satisfy this inclusion criterion.

The following procedures are to be performed and/or data to be collected at Visit 1 (please refer to the schedule of assessments for details):

- Informed consent process
- Confirmation of eligibility criteria
- Height/Weight/BMI
- Complete physical examination
- Medical and asthma history (including prior medication use)
- A record of at least 2 asthma exacerbations within the previous 12 months must also be documented in source prior to enrolment
- ACQ-6 score must be ≥1.5. If this criteria is not met the patient must be screen failed and will not be allowed to rescreen.
- ECG
- Vital signs
- Laboratory assessments (including clinical chemistry, hematology, urinalysis, serum pregnancy test, FSH (if needed) and serology for Hepatitis B, C, HIV-1, HIV-2)

- Reversibility testing - can be performed only in case the patient meets appropriate medication restrictions. If a patient has not met the required medication restrictions or fails the protocol-specified reversibility criterion (≥12% and 200 ml) at Visit 1, further attempts are allowed at Visit 2 or at Visit 3. If participating in the body plethysmography sub-study, the patient must meet reversibility criteria at Visit 1 or 2. No further attempt is allowed at Visit 3

4.1.2 Screening/run-in (Visit 2) Day -21

Assessments applicable for the period are listed in Table 2.

Visit 2 is primarily concerned with evaluating whether lung function meets study eligibility criteria.

Ensure that the patient has met the required medication restrictions. Fractional exhaled NO measurements must be performed prior to any spirometry assessments.

Spirometry - Pre-bronchodilator FEV_1 criterion (<80%) will be tested for the first time at Visit 2. If reversibility testing was not performed at Visit 1 or a patient fails the protocol specified reversibility criterion (≥12% and 200 ml) a second attempt is allowed at Visit 2. For patients participating in the main study only - another attempt is allowed at Visit 3.

The following key procedures are to be performed and/or data to be collected on Visit 2 (please refer to the schedule of assessments for details):

- Revision of inclusion/exclusion criteria
- Collection of adverse events
- Concomitant medication review
- Vital signs measurement
- Fractional exhaled nitric oxide (FeNO) level measurement
- Pulmonary function tests (including Pre-BD FEV_1 testing, reversibility testing, if the reversibility criterion was not met at Visit 1).

4.1.3 Screening/run-in (Visit 3) Day -7

For main study only:

A pre BD FEV_1 should be recorded at Visit 2 as well as at Visit 3, irrespective of whether the patient has met protocol specified pre-bronchodilator FEV_1 criterion (<80%) at Visit 2 or not. If a patient fails the protocol specified reversibility criterion (≥ 12% and 200 ml) at Visit 1 or at Visit 2, a further attempt is allowed at Visit 3.

For sub study only:

Visit 3 is primarily concerned with body plethysmography assessments. Please ensure that all required medication restrictions are adhered to prior to performing these assessments.

A pre BD FEV_1 should be recorded at Visit 2 as well as at Visit 3, irrespective of whether the patient has met protocol specified pre-bronchodilator FEV_1 criterion (<80%) at Visit 2 or not. Please ensure that inclusion criteria #5 and #7 are met prior to performing body plethysmography assessments.

Reversibility testing cannot be performed at Visit 3. This criteria must be met at either Visit 1 or at Visit 2 for those patients participating in the sub-study.

4.1.4 Re-screening

If the reason for screen failure was transient (including but not limited to study-supplied equipment failure or unforeseen personal events that mandate missed screening visits), rescreening can be allowed only once.

Re-screened patient should re-sign informed consent on the re-screening Visit 1. All procedures from screening/run-in period should be repeated.

4.1.4.1 Procedures for patients who experience an exacerbation during screening/run-in

Patients who experience an asthma exacerbation during screening should be treated according to local medical practice. Once the exacerbation has been fully treated and the patient has returned back to their usual maintenance dose and remained on this dose for at least 2 weeks they can be rescreened (only once).

4.2 Treatment period

Inclusion criteria at randomization will be confirmed at Day 0. Adherence to all criteria listed in section 3.3 must be confirmed prior to randomization on Visit 4 (Day 0)

Patients confirmed to be eligible will be randomized at Day 0.

During the Day 0 visit, the patient should complete the following assessments: SGRQ and ACQ-6 completion, and then pre-BD spirometry 60 min and 30 min prior to IP administration.

Patients will be randomized to either placebo or benralizumab 30 mg every 4 weeks throughout the treatment period.

Patients will have more frequently scheduled visits in the 2 weeks after the first IP administration and then more infrequent visits for the rest of study duration (refer Table 3). Restrictions as set out in Section 3.9 will continue to apply throughout the treatment period. In case of an asthma worsening/exacerbation (see Section 4.1.4.1) patients should be evaluated at the study center when feasible.

At Visit 10 (Day 84±7), patients will come to the center for the End of Treatment (EOT) visit.

For patients who prematurely discontinued IP and are not willing to continue to participation in the study refer to Section 3.10 and 3.11.

Completion or early termination of the treatment will be registered via IWRS/IVRS for each patient.

4.3 Follow-up period

Patients who complete the double-blind randomized treatment period will have follow-up visit at Visit 11 (Day 112±7). For study assessments schedule during this visit please refer to Table 3.

5. STUDY ASSESSMENTS

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

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

5.1 Efficacy assessments

5.1.1 Spirometry

General requirements

Lung function (FEV_1 and forced vital capacity [FVC]) at the study center will be measured by spirometry using equipment provided by central vendor. Spirometry will be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005).

The central spirometry vendor is responsible for assuring that the spirometer meets ATS/ERS recommendations and that the study center personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate spirometry procedures manual.

Important! Patients should withhold their SABA medication(s) for at least 6 hours prior to all scheduled lung function assessments. Twice daily LABA- or LAMA-containing therapies should be withheld for 12-24 hours and once daily LABA- or LAMA-containing therapies for >24 hours before spirometry. LTRA should be restricted for >24 hours and twice daily

theophyllines should be withheld for at least 12- 24 hours and once daily for >24 hours before spirometry assessments.

Options for handling patients who have inadvertently taken their asthma medication within the restricted window are described in Section 3.9.1.

Time of day for scheduled center visit spirometry

Spirometry testing should be done initiated in the morning between 6:00 AM and 11:00 AM according to the schedule provided in Table 2 and Table 3. All post-randomization spirometry assessments should be performed within ±1.5 hours of the time at which the qualifying pre-BD FEV_1 spirometry was performed either at Visit 2 or Visit 3.
For example, if the spirometry (pre-BD FEV_1) was started at 08:00 AM at Visit 3 and this spirometry met inclusion #5, then all subsequent spirometry testing needs to be initiated between 06:30 AM and 9:30 AM.

Spirometry technique

Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Patients should avoid eating a large meal for at least 2 hours prior to spirometry measurements at the center. Forced expiratory maneuvers should be performed with the patient seated in an upright position. If this is not comfortable for the patient, standing is permitted. The same position should be used by the patient for each forced expiratory maneuver from enrolment throughout the study. The head must not be tilted during maneuvers and the thorax should be able to move freely; hence, tight clothing should be loosened. A nose-clip should be used for the maneuver. Mouthpieces of the same dimension and shape should be used by the patient from enrollment throughout the study.

The forced expiratory maneuver (FEV_1 and FVC) should start with a maximal inspiration and then followed by a fast and forceful expiration that should last for at least 6 seconds. It is important to encourage the patient to continue the expiration to be fast and forceful throughout the maneuver. Ensure that none of the following has occurred: coughing during the first second, glottis closure, leak or obstruction of the mouthpiece (by the tongue).

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each center spirometry session and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded. The best efforts will be based on the highest FEV_1. The absolute measurement (for FEV_1 and FVC), and the percentage of predicted normal (PN) value (Quanjer et al 2012) 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).

Order of administration of usual asthma controller medication and IP relative to scheduled pre- and post-bronchodilator spirograms

The patient's usual morning asthma controller therapy must not be given until after the exhaled NO and pre-BD spirometry are complete.

For sites participating in the body plethysmography sub-study the usual asthma controller medication must be withheld till all the plethysmography assessments are completed. Investigational product dosing should also be not performed until pre-BD spirometry is complete.

Record keeping

A signed and dated copy of the pre- and post- BD printout must be kept at the study center for source data verification. The printout must be marked with the study code, patient enrolment code, date and time of measurement, and visit number.

Spirometry references

The Global Lung Function Initiative (GLI) equations will be used to determine the patients PN values and are pre-programmed into your spirometer (Quanjer et al 2012).

FEV_1 expressed as percent of the PN value will be calculated as follows:

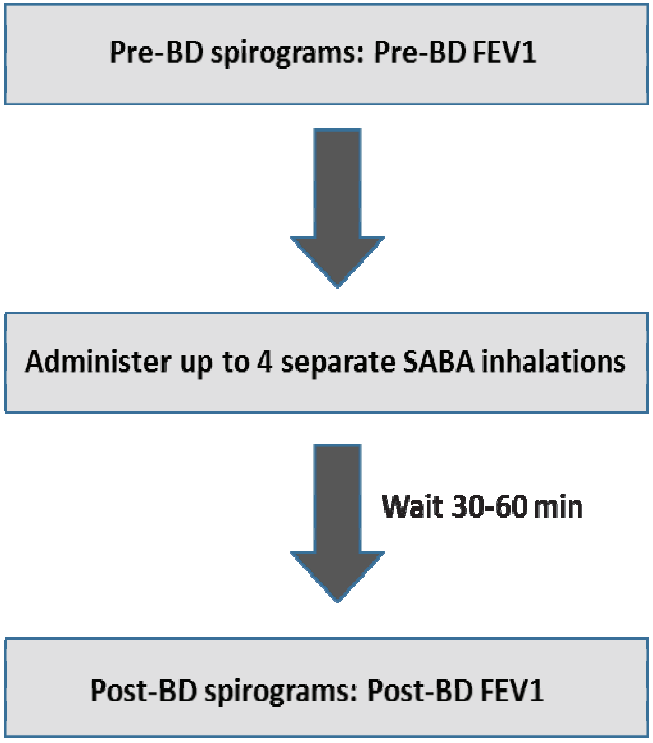
$$FEV_1\% \text{ of } PN = FEV_1 \text{ measured}/FEV_{1PN} \times 100$$

5.1.1.1 Reversibility testing

The procedure described in this section refers to the reversibility testing that can be performed at either Visit 1, Visit 2 or Visit 3. If a patient is participating in the body plethysmography sub-study, reversibility testing can only be performed either at Visit 1 or Visit 2 only.

Bronchodilatation can be induced using albuterol (90 µg metered dose), salbutamol (100 µg metered dose) or levalbuterol (45 µg metered dose) up to a maximum of 4 inhalations). It is highly recommended to use a spacer device for this procedure. The algorithm for reversibility testing is outlined in Figure 3.

Figure 3 Reversibility testing algorithm



1. Verify with the patient the medication restrictions to allow the reversibility assessment have been met (Section 3.8.1)

2. After a gentle and complete expiration, albuterol, salbutamol or levalbuterol is inhaled in one breath to TLC from a spacer device. The breath is then held for 5-10 seconds before the patient exhales. Four separate inhalations are delivered at approximately 30- second intervals. Post-BD spirometry should be performed 30 - 60 minutes later.

3. If the patient has not met reversibility criteria at Visit 1 further attempts to demonstrate reversibility are allowed at Visit 2 and Visit 3 for those patients participating in the main study. For those patients participating in the body plethysmography sub-study only one further attempt is allowed at Visit 2.

A lower total dose, eg, 2 inhalations instead of 4 puffs, can be used if there is a concern about any effect on the patient's heart rate, tremor, or safety.

The highest pre- and post-BD FEV_1 should be used to determine reversibility.

Reversibility is calculated as follows:

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

5.1.2 Fractional exhaled nitric oxide measurement

Airway inflammation will be evaluated using a standardized single-breath fractional exhaled nitric oxide (FeNO) test (ATS 2005).

Since spirometry can potentially impact the nitric oxide 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.

While sitting, subjects are to inhale to total lung capacity through the NIOX MINO® Airway Inflammation Monitor (Aerocrine, New Providence, New Jersey) and then exhale for 10 seconds at 50 mL/sec (assisted by visual and auditory cues). The value obtained will be recorded and the process repeated twice for a total of 3 measurements. The 3 measurements will be printed to serve as a source document.

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

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Safety laboratory tests (list provided in Table 4 below) will be performed in a central laboratory. For information on methods of collection, assessment, labelling, storage, and shipment of samples please refer to the separate Laboratory Manual. Safety samples will be collected in accordance with the schedules provided in Table 2 and Table 3.

Hematology and urinalysis will be assessed in line with the schedules provided in Table 2 and Table 3.

The following laboratory variables will be measured:

Table 4 Laboratory safety variables

Hematology/hemostasis (whole blood)	Clinical chemistry (serum or plasma)	Urinalysis
Hematocrit	Alkaline phosphatase (ALP)	Appearance
Hemoglobin (Hb)	Aspartate transaminase (AST)	Blood
Mean corpuscular volume (MCV)	Alanine transaminase (ALT)	Color
Platelet count	Blood urea nitrogen (BUN)	Ketones
Red blood cell (RBC)	Calcium	Microscopy including WBC/high power field (HPF), RBC/HPF
White blood cell (WBC) count with differential	Chloride	pH
	Creatinine	Specific gravity
	Gamma-GT (gamma-glutamyl transpeptidase)	
	Glucose	
	Phosphorus	
	Potassium	
	Sodium	
	Bilirubin, total	
	Cholesterol, total	
	Uric acid	

a Eosinophils, basophils and monocytes counts will be redacted from central laboratory reports except for Visit 1 (see Section 3.7).

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a subject shows an AST **or** ALT ≥3xULN **and** total bilirubin ≥2xULN please refer to Appendix D 'Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law', for further instructions.

5.2.1.1 Pregnancy test

The following tests are applicable to female patients only and will be conducted in accordance with the schedules provided in Table 2 and Table 3.

- Serum beta-hCG: To be done at screening Visit 1, Visit 10 and premature IP discontinuation visit (IPD), for WOCBP (analyzed at central laboratory)

- FSH: To be done at screening Visit 1 only, for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for ≥12 months

- Urine HCG: To be performed at the study center for WOCBP at each treatment visit (before IP administration on Visit 4, Visit 8, Visit 9, Visit 10, IPD and Visit 11) using a dipstick. A positive urine test result must be confirmed with serum beta HCG.

5.2.2 Physical examination

Physical examination will be done in accordance with the schedules provided in Table 2 and Table 3.

Baseline data will be collected at Visit 1. Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE as described in Section 6.3.

5.2.2.1 Complete physical examination

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems.

5.2.2.2 Brief physical examination

The brief physical examination includes an assessment of the general appearance, abdomen, cardiovascular, and respiratory system. For the brief physical examination only information on whether the assessment was performed or not is to be recorded.

5.2.3 Electrocardiogram

5.2.3.1 Resting 12-lead electrocardiogram

Electrocardiograms (ECG) are to be performed in accordance with the schedule provided in Table 2 and Table 3.

A 12-lead ECG will be taken in supine position, after the patient has been resting for at least 5 minutes. The assessment should be performed before interventions with the patient (eg, spirometry and administration of the asthma-related medications and IP).

The Investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. In case of discrepancy between the Investigators interpretation and that provided by the ECG machine (if applicable), the Investigator's interpretation takes precedence and should be noted on the printout and recorded in the eCRF. Two identical copies of the ECG will be produced, quality checked,

and kept in case of further need for re-evaluation. The ECG printouts will be signed and dated by the Investigator and stored at the study center.

ECG data and evaluation will be recorded in the eCRF.

5.2.4 Vital signs

5.2.4.1 Pulse and blood pressure

Pre-dose vital signs (pulse, blood pressure, respiration rate, and body temperature) are to be obtained in accordance with schedule provided in Table 2 and Table 3

Vital signs are to be taken prior to IP administration, and, if possible, before blood drawing and usual asthma controller medication. Vital signs should also be taken prior to bronchodilator administration if applicable for that visit.

5.2.4.2 Body temperature

Body temperature is to be recorded in degrees Celsius.

5.3 Other assessments

5.3.1 Weight and height

Weight and height will be measured, and BMI calculated in accordance with schedules provided in Table 2.

The patient's weight will be recorded in kilograms; height will be recorded in centimeters.

Weight and height measurements will be performed in light clothing and with shoes off.

5.3.2 Patient reported outcomes

Patients will complete patient-reported outcome (PRO) assessments using a tablet ePRO device at the site. Patients will complete a training module prior to the first assessment to ensure that they understand how to use the device.

PRO assessments should be done before other visit procedures.

5.3.2.1 Asthma Control Questionnaire

The ACQ-6 is a shortened version of the Asthma Control Questionnaire (ACQ) that assesses asthma symptoms (nighttime waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and short-acting β2 agonist use) omitting the FEV_1 measurement from the original ACQ score.

Patients are asked to recall how their asthma has been during the previous week by responding to 1 bronchodilator use question and 5 symptom questions.

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤0.75

indicate well-controlled asthma, scores between 0.75 and ≤1.5 indicate partly controlled asthma, and a score >1.5 indicates not well controlled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered to be clinically meaningful.

By omitting the ACQ-6 bronchodilator use question from the scoring algorithm, an ACQ-5 score can be calculated.

The questionnaire will be completed at the study center via provided site tablet (ePRO) in accordance with schedule provided in Table 2 and Table 3

5.3.2.2 St. George's Respiratory Questionnaire

The St. George's Respiratory Questionnaire (SGRQ) is a 50-item PRO instrument developed to measure the health status of subjects with airway obstruction diseases (Jones et al 1991). The questionnaire is divided into 2 parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and 3 domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment. Specific details on the scoring algorithms are provided by the developer in a user manual (Jones et al 2009).

5.3.2.3 Patient Global Impression of Severity assessments

The Patient Global Impression of Severity (PGI-S) is a single item designed to capture the patient's perception of overall symptom severity at the time of completion using a 6-point categorical response scale (no symptoms to very severe symptoms). For the time of completion, refer to Table 3.

The PGI-S should be completed on the site tablet by the patient before other study assessments and IP administration per the schedule provided in Table 3

5.3.2.4 Clinician and Patient Global Impression of Change assessments

Clinician Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C) instruments are used for an overall evaluation of response to treatment. The Investigator (clinician) and the patient will be asked to rate the degree of change in the overall asthma status compared to the start of treatment, ie, randomization visit. A 7-point rating scale will be used: 1= Very Much Improved; 2= Much Improved; 3= Minimally Improved; 4= No Changes; 5=Minimally Worse; 6=Much Worse and 7= Very Much Worse.

The CGI-C and PGI-C should be completed on the site tablet by the patient before other study assessments and IP administration per the schedule provided in Table 3

5.3.3 Other screening/run-in assessments

5.3.3.1 Serology

Hepatitis B surface antigen, hepatitis C antibody: To be done only at enrolment (Visit 1); test to be performed at central laboratory.

HIV-1 and HIV-2 antibodies: To be done only at enrolment (Visit 1); test to be performed at central laboratory.

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

5.3.3.2 Serum immunoglobulin E

The levels of total immunoglobulin E (IgE) will be evaluated by a central laboratory. These tests will be performed at Visit 4 (Week 0) (see Table 3).

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

5.3.4 Pharmacokinetics

5.3.4.1 Collection of samples

For the PK analysis it is important that the date and time of each SC injection is recorded for each patient.

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

Serum will be collected every visit from Visit 4 to Visit 10. On the dosing days, ie, Visit 4, 8 and 9, the serum will be collected as pre-dose.

5.3.4.2 Determination of drug concentration

Samples for determination of drug concentration in serum will be analyzed by a central laboratory on behalf of AstraZeneca, using a validated bioanalytical method. Full details of the analytical method used will be described in bioanalytical report.

5.3.4.3 Storage and destruction of pharmacokinetic samples

The PK samples will be retained at AstraZeneca or designee for a maximum of 3 years following publication of the CSR to properly address potential questions from regulatory authorities (RAs).

A summary of PK analysis results will be reported in the Clinical Study Report (CSR).

5.3.5 Pharmacodynamics

5.3.5.1 Collection of samples

Samples for the analysis of peripheral blood eosinophils will be performed in a central laboratory as part of the routine hematology assessment (complete blood count [CBC]).

5.3.5.2 Immunogenicity

Instructions for immunogenicity (ADA and nAb) sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centers.

The immunogenicity samples will be retained at AstraZeneca or designee for a maximum of 3 years following publication of the CSR to properly address potential questions from RAs.

A summary of the analysis will be presented in the CSR. Details of the analytical method used will be described in a bioanalytical report.

5.3.5.3 Anti-drug antibodies

Serum samples for analysis of anti-drug antibodies (ADA) will be collected pre-dose at selected visits according to the study plan (see Table 3).

The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods.

5.3.5.4 Neutralizing antibodies

In vitro neutralizing antibody (nAb) activity is to be tested at all ADA collection time points of Week 16 and later in samples that are ADA-positive. Samples that are ADA-negative will not be tested for nAb.

The presence or absence of neutralizing antibodies will be determined using a validated bioanalytical method.

5.3.6 Pharmacogenetics

Pharmacogenetic samples will not be taken during the study

5.3.7 Biomarker analysis

Samples for biomarker analysis will not be collected during the study.

5.3.8 Handling of biological samples

5.3.8.1 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

5.3.8.2 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each center keeps full traceability of collected biological samples from the subjects while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival (where applicable).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

5.4 Additional assessments applicable for the subset of subjects – body plethysmography sub-study

Additional assessments will be performed for a subset of subjects at designated sites, approximately 50 subjects in the study, to determine the effect of benralizumab on the time course of change in lung function as assessed through body plethysmography.

Patients who participate in the sub-study will perform other lung function assessments as mentioned in sections 4.1.1, 4.1.2, 4.1.3, 4.2 and 4.3.

5.4.1 Body plethysmography

Body plethysmography is to be performed only by sites participating in the body plethysmography sub-study and will be performed on approximately 50 patients.

Lung volume subdivisions which include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC), as well as airway resistance (Raw and SGaw) measurements, 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 (see Table 2 and Table 3).

Lung volumes will be determined by body plethysmography. The test will be performed by qualified pulmonary function technicians with experience performing this assessment. 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.

It is expected that medication restrictions required for spirometry assessments (see section 3.9) are met for body plethysmography too. To enable that, body plethysmography assessments should be done soon after pre-BD spirometry assessments are complete, and before medications are given to patient.

Each site is expected to use their own body boxes to conduct assessments provided they meet the quality and experience criteria set by AstraZeneca. Details related to this procedure are provided in a separate body plethysmography manual provided to the designated study centers.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg. nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, wash-out, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent 1 of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix B to the clinical study protocol (CSP).

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period (through Day 112 [±7days]).

Serious adverse events will be recorded from the time of informed consent.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at follow-up in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the case report form (CRF). AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity of the AE
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study *(*yes or no*)*
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization

- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory

values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.6.1 Symptoms of the disease under study

6.3.7 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3xULN together with total bilirubin ≥2xULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Disease progression

When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. Asthma symptoms or signs, such as wheeze, cough, chest tightness, dyspnea, breathlessness and phlegm, will be recorded as AEs only when:

- The sign or symptom is serious according to definitions, see Section 6.1
- The patient discontinues the study due to the sign or symptom
- The sign or symptom is new to the patient or not consistent with the patient's pre-existing asthma history (defined as within 1 year of Visit 1) as judged by the Investigator.

Asthma exacerbation should be recorded as an AE or SAE only if it fulfills any of the above criteria.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the Investigator's Brochure (IB) for the AstraZeneca drug.

6.5 Overdose

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 16 weeks (5 half-lives) following the last dose.

Pregnancy of the patient's partners will not be considered an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented for conceptions occurring from the date of the first administration of IP until 16 weeks (5 half-lives) after the last administration of IP.

6.7 Management of investigational product-related reactions

Appropriate drugs (eg, epinephrine, H1 and H2 antihistamines, and corticosteroids), and medical equipment to treat acute anaphylactic reactions must be immediately available. Study personnel must be trained to recognize and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix F.

Anaphylaxis will be defined as a serious reaction that is rapid in onset and may cause death (Simpson et al 2006). Anaphylaxis typically manifests as 1 of 3 clinical scenarios:

1. The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both, and at least 1 of the following: a) respiratory compromise or b) reduced blood pressure or symptoms of end-organ dysfunction

2. Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms and/or persistent gastrointestinal symptoms

3. Reduced blood pressure after exposure

Patients will have had a pre-assessment (ie, vital signs and lung function) prior to IP administration) and should be observed after IP administration for a minimum of 2 hours for the appearance of any acute drug reactions.

In order to help understand the potential drug-relatedness of any acute reaction, a blood sample should be drawn during the event for possible additional ADA testing (if not already scheduled for this visit). Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the Investigator.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

All investigational products will be manufactured in accordance with Good Manufacturing Practice (GMP).

Benralizumab and placebo administered in the study will be a clear to opalescent, colorless to yellow solution

Investigational product	Dosage form and strength	Manufacturer
Benralizumab	30 mg/mL solution for injection in accessorized pre-filled syringe, 1 mL fill volume	MedImmune
Placebo	Matching placebo solution for injection in accessorized pre-filled syringe, 1 mL fill volume	MedImmune

7.2 Dose and treatment regimens

The IP will be administered at the study center on treatment visits and within visit windows as specified in Table 3.

Before investigational product administration

Prior to each IP administration:

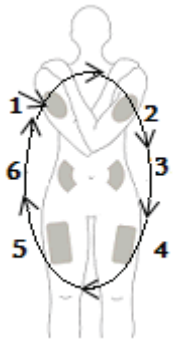
- Investigator/authorized delegate will assess injection site as per standards of medical care

- For WOCBP, urine pregnancy test will be done; IP will be administered only when the result of the test is negative (see Section 5.2.1.1)

Investigational product administration

The IP will be administered by the Investigator/authorized delegate. It is advised that the site of injection of the IP be rotated such that the patient receives IP at a different anatomical site at each treatment visit. Suggested injection site rotation sequence is presented below (see Figure 4).

Figure 4 Injection sites and rotation scheme



In the case when rotation of the injection site is not favorable for the patient and/or Investigator, the reason should be recorded in the source documents. The injection site of the IP should be recorded in the source documents and eCRF at each treatment visit.

Further details on IP administration are provided in the IP Handling Instruction. Investigational product administration must be carried out in line with the Instruction.

After investigational product administration

After IP administration the patient should be observed for a minimum of 2 hours for the appearance of any acute drug reactions.

Conditions requiring investigational product administration rescheduling

If any of the following occur, the Investigator should reschedule the visit and the IP should not be administered until the rescheduled visit:

- The patient has an intercurrent illness, that in the opinion of the Investigator may compromise the safety of the patient in the study (eg, viral illnesses)

- The patient, in the opinion of the Investigator, is experiencing an acute or emerging asthma exacerbation

- The patient is febrile (≥38°C; ≥100.4°F) within 72 hours prior to the IP administration

7.3 Labelling

Labelling of the IP will be carried out by AstraZeneca or desingee in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines of each country participating in the study. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

The label will include the following information:

- study code

- Investigational product/study drug dosage form, route of administration and quantity of dosage units

- kit ID

- P Lot ID

- Expiry date

- Investigator Name (to be written on the label)

- E-code (to be written in the label)

- Sponsor name and contact details

- Directions for use

- Storage condition

- Standard statements required by regulatory authorities

7.4 Storage

Benralizumab/placebo is to be stored at the study center in a secured facility with limited access and controlled temperature. The temperature should be monitored on a daily basis and documented in the temperature monitoring log.

The IP must be kept in the original outer container and under conditions specified on the label (between 2-8°C (36-46°F), protected from the light).

In the following cases the center staff should not use affected IP and should immediately contact an AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study
- Damaged kit upon receipt
- Damaged syringe/cartridge

Damaged IP should be documented via IWRS/IVRS (refer to IWRS/IVRS manual for further details).

7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the CRF.

The IP will be administered at the study center on treatment visits and within visit windows as specified in Table 3.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to the subject.

The monitor will account for all study drugs received at the center, unused study drugs and for appropriate destruction. Certificates of delivery, destruction, and/or return should be signed.

In the case of a malfunctioning accessorized prefilled syringe (APFS), the center should contact the study monitor to initiate a product complaint process according to applicable guidelines.

7.7 Concomitant and other treatments

Information about any treatment in the 3 months prior to the date of the informed consent, and all the concomitant treatments given during the study with reason for the treatment will be collected by the Investigator/authorized delegate at each visit (as shown in Table 2 and Table 3) and recorded in the eCRF.

Note: To satisfy inclusion criterion 3 (Section 3.1), the history of treatment with asthma therapies at the protocol designated doses prior to Visit 1 should be documented in source and recorded in the eCRF.

7.7.1 Background medication

All patients are required to be treated with stable dose ICS/LABA for at least 30 days prior to Visit 1 and during the course of the study. For ICS/LABA combination preparations, high-strength maintenance doses approved in the local country will meet this criterion. If the ICS and LABA therapies are given by separate inhalers, the ICS dose must be >500 µg fluticasone proprionate dry powder formation or equivalents daily.

The background asthma controller medications should be maintained at a stable dose from Visit 1 until the end of the study. No changes are allowed to background medications throughout the duration of the study except during the treatment of an asthma exacerbation.

7.7.2 Rescue medication

Short-acting bronchodilators (SABAs) may be used as rescue medication during the study in the event of a worsening of asthma symptoms.

7.7.3 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.

Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first subject randomized and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

8.2 Sample size estimate

The study is powered for the primary objective of the study to determine the effect of benralizumab on the time course of change (onset and maintenance of effect) of pre-BD FEV_1. The first post baseline timepoint where the p-value for the mean difference between benralizumab and placebo is less than or equal to 0.05 will be used to determine time to onset of effect. The average over the mean differences between benralizumab and placebo based on the change from baseline (Visit 4) to Days 28 (Visit 8), 56 (Visit 9) and 84 (Visit 10) in pre-BD FEV_1 will be used to determine if the study is positive as well as maintenance of effect.

The benralizumab Phase 2b study MI-CP220 (Castro et al 2014) as well as results from the benralizumab Phase 3 asthma exacerbation studies were used as a basis for the sample sizing. From these studies, it is expected that around 115 patients per treatment arm (230 in total) will provide approximately 90% power for the primary endpoint pre-BD FEV_1 with type I error controlled at a two-sided alpha level of 0.05 if the true average over the mean treatment differences (benralizumab – placebo) across Days 28 (Visit 8), 56 (Visit 9) and 84 (Visit 10) is 138 mL. The sample size will also be sufficient to have approximately 80% power for an average over the mean treatment difference of 120 mL. The assumed variability has a within group standard deviation of 375 mL and within subject correlation of 0.6. If the within

subject variability is reduced to 350 mL the sample size would be sufficient to have 80% power for an average of 110 mL. In addition, it is expected that around 115 patients per treatment arm will have 80% power to detect a true treatment difference (benralizumab – placebo) of 130 mL assuming a within-group standard deviation of 350 ml or a true treatment difference of 140 mL assuming a standard deviation of 375 mL. Based on these assumptions, the minimum difference that would be statistically significant at the 0.05 level range from approximately 85 to 100 mL. The sample size was estimated using nQuery+nTerim version 3.0 using methodology in (Liu et al 2005)

8.3 Definitions of analysis sets

All efficacy will be performed according to the Intent-to-Treat (ITT) principle based on the full analysis set. For consistency, demographic and baseline characteristics will be presented using the full analysis set. Safety objectives will be analyzed based on the safety analysis set.

8.3.1 All patients analysis set

This analysis set will comprise all patients screened for the study and will be used for reporting of disposition and screening failures.

8.3.2 Full analysis set

All patients randomized and receiving any IP will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the ITT principle. Patients who withdraw consent, and assent when applicable, to participate in the study will be included up to the date of their study termination.

8.3.3 Body plethysmography sub-study analysis set

The subset of patients who are randomized as part of the body plethysmography sub-study and receive any IP will be analyzed as described for the full analysis set.

8.3.4 Safety analysis set

All patients who received at least 1 dose of IP will be included in the safety analysis set. Patients will be classified according to the treatment they actually received. A patient who has on 1 or several occasions received active treatment will be classified as active. All safety summaries will be based on this analysis set

8.3.5 Pharmacokinetic analysis set

All patients who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations and who had at least 1 quantifiable serum PK observation post first dose will be included in the PK analysis dataset. All PK summaries will be based on this analysis set.

8.4 Outcome measures for analyses

Definition of baseline

In general, the last measurement prior to the first dose of study treatment will serve as the baseline measurement. If time is collected, assessments performed the same day but at a time prior the first dose of study treatment will be included in baseline definition. If there is no value prior to the first dose of study treatment, then the baseline value will not be imputed and will be set to missing.

Visit 4 is the planned baseline visit, for all assessments carried out at a center, except for physical examination. The baseline visit for physical examination will be Visit 1.

The pre-BD FEV_1 measurement recorded at Visit 4 will be used as baseline FEV_1. If the Visit 4 pre-BD measurement is missing, the last non-missing pre-BD value before Visit 4 will be used as baseline instead.

Change from baseline will be calculated as the post-baseline assessment value minus the baseline assessment value. If either value is missing, then the change from baseline value will be missing.

8.4.1 Calculation or derivation of efficacy variables

All efficacy objectives will be evaluated for the double-blind treatment period, defined as the period after administration of randomized IP at Visit 4 and the conclusion of EOT visit, inclusive.

8.4.1.1 Pre-bronchodilator forced expiratory volume in 1 second

Time to onset of effect in Pre-BD FEV_1 is the primary objective of this study. The mean change from baseline to each of the post-randomization visits (post Visit 4) up to and including the end of double-blind treatment visit at day 84 (Visit 10) of pre-BD FEV_1 will be the primary efficacy variable of this study.

8.4.1.2 Eosinophils counts in the blood

Eosinophil counts in the blood as well as percentage change from baseline (Visit 4) at each post-baseline visit will be secondary efficacy variables for this study. These variables will also be used to assess the treatment effect over time of eosinophils in the blood.

8.4.1.3 Forced vital capacity

The mean change from baseline (Visit 4) in FVC to each of the post-baseline visits will be a secondary efficacy variable for this study.

8.4.1.4 Asthma Control Questionnaire

The change in mean score from baseline (Visit 4) in ACQ-6 to each of the post-randomization periods will be a secondary efficacy variable for this study.

Patients will also be categorized according to the following limits (Juniper et al 2005):

- ACQ-6 (End of treatment –baseline) ≤-0.5 → Improvement
- 0.5<ACQ-6 (End of treatment –baseline) <0.5 → No change
- ACQ-6 (End of treatment –baseline) ≥0.5 → Deterioration.

An ACQ-6 responder will be defined as a patient who had improvement on ACQ-6, ie, an ACQ-6 responder variable takes value 1 if change from baseline to end of treatment in ACQ-6 ≤-0.5 and 0 otherwise.

Furthermore, patients will be categorized according to their ACQ-6 end of treatment score as follows (Juniper et al 2006):

- ACQ-6 (End of treatment) ≤0.75 → Well controlled
- 0.75<ACQ-6 (End of treatment) <1.5 → Partly controlled
- ACQ-6 (End of treatment) ≥1.5 → not well controlled

8.4.1.5 St. George's Respiratory Questionnaire

The change in mean total score in SGRQ from baseline (Visit 4) to each of the post-randomization periods in total score will be a secondary efficacy variable for this study.

For the responder analysis of SGRQ a responder will be defined as an individual with a ≥4-point decrease (improvement) in SGRQ total score.

8.4.1.6 Exhaled nitric oxide

The mean change from baseline (Visit 4) of FeNO to each post-baseline visit will be a secondary efficacy variable for this study.

8.4.1.7 Patient Global Impression of Severity

Patient Global Impression of Severity (PGI-S) is a single question asking the patient to rate the severity of their symptoms using a 6-point categorical response scale (0=no symptoms, 5=very severe symptoms). Improvement using the PGI-S will include changes from moderate, severe, and very severe to no symptoms, very mild, mild as well as patients who have improvements in their responses from baseline.

8.4.1.8 Patient and Clinician Global Impression of Change

Clinician Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C) instruments are used for an overall evaluation of response to treatment. The Investigator (clinician) and the patient will be asked to rate the degree of change in the overall asthma status compared to the start of treatment, ie, randomization visit. A 7-point rating

scale will be used: 1=Very Much Improved; 2=Much Improved; 3=Minimally Improved; 4=No Changes; 5=Minimally Worse; 6=Much Worse and 7=Very Much Worse.

The clinician and patient will be asked, separately, to rate the degree of change in the overall asthma status compared to the randomization visit. Calculation of percentages will be based on the number of subjects in the full analysis set with a completed assessment. There will be no imputation for missing values.

Patients will also be categorized according to the following responses post-baseline, separately for both the CGI-C and PGI-C:

- Very much improved, much improved, minimally improved → Improved
- Very much improved, much improved → Much improved
- Very much improved → Very much improved

8.4.2 Body plethysmography sub-study

8.4.2.1 Body lung function as assessed through body plethysmography

The mean change from baseline to each of the post-randomization visits (post Visit 4) up to and including the end of 12-week double-blind treatment visit (Visit 10) will be used as efficacy variables within the body plethysmography sub-study analysis set. The level recorded at Visit 4 will be used as baseline. The primary variable for the sub-study will the change from baseline in residual volume (RV). Secondary variables for the sub-study will be the change from baseline in total lung capacity (TLC), RV/TLC ratio, vital capacity (VC), inspiratory capacity (IC) and functional residual capacity (FRC). Other variables for the sub-study are SGaw and Raw.

8.4.3 Calculation or derivation of safety variable(s)

8.4.3.1 Safety variables

The following safety data will be collected: vital signs, physical examination and ECG, haematology, clinical chemistry, urinalysis, reported AEs and SAEs.

8.4.4 Calculation or derivation of pharmacokinetic variables

Summary statistics of the PK will be generated for each visit where serum samples are collected. In addition, estimation of PK parameters, ie, C_{max}, t_{max}, and $AUC_{[0,28d]}$ will be computed for the first dosing cycle using noncompartmental estimation method. C_{max} and T_{max} are direct measurements of the maximum observed concentration and the time to reach the C_{max} respectively during the first dosing cycle.

8.4.5 Calculation or derivation of immunogenicity variables

Assessments of anti-drug antibodies (ADA) will be conducted using a tiered approach (screen, confirm, titer). The presence of in vitro neutralizing antibody (nAb) activity will be tested in all ADA-positive samples time points using a ligand binding assay.

8.5 Methods for statistical analyses

Demographics and subject characteristics will be summarized by treatment group using frequency and percentages (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median and maximum (for continuous variables) using the full analysis set.

The analysis of the primary and secondary endpoints will include all data captured during the 84-day treatment period, including follow-up (where applicable), unless the patient withdraws consent to study participation, regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence. To emphasize the importance of collecting complete primary and secondary outcome data in all patients, the informed consent form (ICF) form will ask that patients continue study assessments for the whole 84-day double-blind treatment period, including follow-up, even if they discontinue study treatment prematurely.

Descriptive statistics will also be provided for safety and efficacy data. Unless otherwise stated, the data analysis include subjects in the full analysis set. Descriptive statistics on continuous variables will be summarized by treatment group using mean, standard deviation, minimum, median and maximum, while categorical data were summarized using frequency counts and percentages. When data are summarized by time, the values recorded against the scheduled time points listed in the protocol will be used. When assessing minimum/maximum increases or decreases during the study, all assessments, including unscheduled assessments will be used. For analysis assessing change from baseline, only subjects with both baseline and at least 1 evaluable post-baseline measure will be included.

Given there is a single primary endpoint and treatment comparison no formal testing strategy will be used for the analysis in this study.

The prior medications, categorized according to the WHO Drug Reference List dictionary which employs the Anatomical Therapeutic Chemical (ATC) classification system, will be summarized by treatment group as frequency and percentage of subjects reporting usage.

The concomitant medication will be categorized according to the WHO Drug Reference List dictionary which employs the Anatomical Therapeutic Chemical (ATC) classification system. The frequency and percentage of subjects taking concomitant medications and non-drug therapies during the treatment period will be summarized by drug class and drug name using ATC code.

8.5.1 Analysis of the primary variable(s)

The change from baseline in pre-BD FEV_1 up until the EOT at Visit 10 will be compared between the 30 mg benralizumab group and placebo using a repeated measures analysis on patients with a baseline pre-BD FEV_1 and at least 1 post-randomization pre-BD FEV_1 in the full analysis set. The dependent variable will be the change from baseline in pre-BD FEV_1 at post-baseline protocol specific visits (up to and including the EOT Visit). Treatment group will be fitted as the explanatory variable, region, visit and treatment*visit interaction as fixed

effects and baseline pre-bronchodilator FEV1 as a covariate. The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is:

*Change in FEV_1=Treatment group+ baseline pre-BD FEV_1+ region + visit+ treatment*visit*

The primary objective of the study is to determine the effect of Benralizumab on the time course of change (onset and maintenance of effect) of pre-BD FEV_1 using the model described above. The first post baseline timepoint where the p-value for the mean difference between benralizumab and placebo is less than or equal to 0.05 will be used to determine time to onset of effect. The average over the mean differences between benralizumab and placebo based on the change from baseline (Visit 4) to Days 28 (Visit 8), 56 (Visit 9) and 84 (Visit 10) in pre-BD FEV_1 will be used to determine if the study is positive as well as maintenance of effect. Contrasts will be used to obtain estimates of the treatment differences over Days 28, 56 and 84 as well as at each timepoint separately.

Additional supportive analyses to the primary objective of the study will be carried out as detailed below.

The modelled treatment response as well as differences between benralizumab and placebo using the mean change from baseline in pre-BD FEV_1 endpoint using an exponential model over time will be estimated. The model will be used determine the modelled time to onset of effect where the pre-BD FEV_1 reaches thresholds for improvement in both mean differences between benralizumab and placebo as well as within treatment change from baseline differences. If the exponential model does not fit the time profile alternative models will be assessed.

The first timepoint using the repeated measures analyses where the observed mean treatment difference between benralizumab and placebo is first greater than different thresholds for improvement will also be presented. In addition for each treatment group time to event analyses will be carried out to present the proportion of patients with onset of effect over time using different within patient change from baseline thresholds.

8.5.2 Analysis of the secondary variable(s)

8.5.2.1 Analysis methods for secondary efficacy variables

Secondary efficacy variables in this study include:

- Absolute and percentage change from baseline of peripheral blood eosinophil counts until EOT at Visit 10
- Change from baseline in FVC until EOT at Visit 10
- Change from baseline in ACQ-6 score until EOT at Visit 10
- Change from baseline in SGRQ score until EOT at Visit 10

- Change from baseline in FeNO (ppb) until EOT at Visit 10

For each variable, the objective is to determine the effect of benralizumab on the time course of change (onset and maintenance of effect).

Other variables include:

- Change from baseline in Patient Global Impression of Severity until EOT at Visit 10
- Patient and Clinical Global Impression of Change until EOT at Visit 10

For the following variables:

- Peripheral blood eosinophil counts
- Exhaled nitric oxide (FeNO)
- FVC
- ACQ-6 score
- SGRQ
- Change from baseline in PGI-S as a continuous measure.

The change from baseline at each timepoint will be compared between benralizumab and placebo using a repeated measures analysis. The dependent variable will be change from baseline for each endpoint. Treatment group will be fitted as the explanatory variable, region, visit and treatment*visit interaction as fixed effects and corresponding baseline as a covariate. The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge the compound symmetric variance-covariance matrix will be used instead. The least squares mean for the difference in treatment groups using the interaction between visit and treatment group its 95% CI, and the 2-sided p-values will be reported for each post baseline visit.

As for the primary endpoint the first post baseline timepoint where the p-value for the mean difference between benralizumab and placebo is less than or equal to 0.05 from the repeated measures analysis will be used to determine time to onset of effect. The average over the mean differences between benralizumab and placebo based on the change from baseline (Visit 4) to Days 28 (Visit 8), 56 (Visit 9) and 84 (Visit 10) will be used to determine maintenance of effect. Contrasts will be used to obtain estimates of the average treatment differences over Days 28, 56 and 84 as well as for each timepoint separately.

In addition supportive analyses to using the modelled treatment difference between benralizumab and placebo using the mean change from baseline as well as the first timepoint using the repeated measures analyses where the observed mean treatment difference between

benralizumab and placebo are first greater than different thresholds for improvement will be presented.

Patients with a CGI-C improved, much improved and very much improved will be analysed using a logistic regression model with covariates of treatment and region. The percentage and number of patients in each category for these endpoints will also be summarised over time. This analysis will be repeated for the PGI-C well as for those patient with have an improvement using the PGI-S. In addition the number and percentage of patients within each of the PGI-S, CGI-C and PGI-C categories as well as a shift tables demonstrating how patients change their categories throughout the study will be presented.

As supportive analyses to the repeated measures analyses the responder variables for ACQ-6 and SGRQ will be analyzed as for the PGI-C, CGI-C and PGI-S endpoints.

8.5.2.2 Analysis for the Body plethysmography sub-study

For the body plethysmography sub-study the primary efficacy variable is the change from baseline in body lung function RV as assessed through body plethysmography until EOT at Visit 10

Secondary efficacy variables for the body plethysmography sub-study are:

- Change from baseline in body lung function (TLC, RV/TLC ratio, VC, IC, and FRC) as assessed through body plethysmography until EOT at Visit 10

Other endpoints for the body plethysmography sub-study are change from baseline in SGaw and Raw.

These endpoints will be analysed as for the primary endpoint however in the subset of patients in the body plethysmography sub-study population.

8.5.2.3 Analysis of the safety variables

Adverse events will be coded using the MedDRA dictionary. Number of subjects with events and percentages will be tabulated by preferred term and system organ class. An event that occurred once or more times during the study treatment period will contribute 1 observation to the numerator of the proportion. The denominator of the proportion will comprise all subjects in the Safety set. Adverse events will also be summarized by intensity/severity and separately, by causality/relatedness (as determined by the investigator). Should a subject report the same preferred term/system organ class within multiple intensity/severity or causality/relatedness categories, the subject's worst occurrence (most severe/most related) will be tabulated. Serious AEs, AEs leading to discontinuation, and commonly occurring AEs will be summarized in a generally similar manner. Adverse events, SAEs, AEs leading to death, and AEs leading to study discontinuation will be summarized for each treatment group as applicable.

Laboratory data will be summarized by presenting shift tables using normal ranges (baseline to most extreme post-baseline value) and by presenting summary statistics of observed and change from baseline values (means, medians, quartiles, ranges). The incidence of clinically notable lab abnormalities will be summarized.

Vital sign data will be summarized by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable vital sign abnormalities will be summarized.

Electrocardiogram intervals will be summarized by presenting summary statistics of observed and change from baseline values. The (uncorrected) QT interval will be corrected according to the Fridericia's formula. The incidence of clinically notable ECG abnormalities will be summarized.

8.5.3 Subgroup analysis

Full details of subgroup analyses will be pre-specified in the SAP.

8.5.4 Interim analysis

No interim analyses are planned.

8.5.5 Sensitivity analysis

Full details of any sensitivity analysis will be pre-specified in SAP.

8.5.6 Exploratory analysis

The exploratory analysis of the PK of benralizumab in sputum will be analysed and reported outside of the CSR.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and WBDC, IWRS/IVRS, ePROs, and other systems to be utilized.

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

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

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

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

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

9.2.1 Source data

Refer to the clinical study agreement (CSA) for location of source data.

9.2.2 Recording of data

A Web-based Data Capture (WBDC) system will be used for data collection and query handling. Trained study center personnel will be responsible for entering data on the observations, tests, and assessments specified in the CSP into the WBDC system and according to eCRF instructions. The eCRF instructions will also guide the study center in performing data entry.

Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be source data verified, reviewed/queried and updated as needed. The data will be validated as defined in the Data Management Plan. The Investigator will ensure that data are recorded on the eCRFs as specified in the CSP and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the CSA. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study center.

9.2.3 Study agreements

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

Agreements between AstraZeneca and the PI should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.4 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study is expected to start in Q3 2016 and to end by Q4 2017.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with benralizumab.

9.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Centre staff according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the data management plan (DMP). Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable

and have been processed correctly. The DMP will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious adverse event reconciliation

Serious adverse event reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

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

10.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final study protocol, including the final version of the ICFand any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The EC should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC annually.

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

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

AstraZeneca will provide RAs, ECs, and PIs with safety updates/reports according to local requirements.

Each PI is responsible for providing the ECs/institutional review boards (IRBs) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the PI so that he/she can meet these reporting requirements.

10.4 Informed consent

The PI(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an EC.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International Coordinating Investigator AstraZeneca.

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

The amendment is to be approved by the relevant EC and if applicable, also the national RA approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI(s). For distribution to EC, see Section 10.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's EC are to approve the revised ICF before the revised form is used.

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

10.6 Audits and inspections

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

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Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B

- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations

- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging

- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 6.3.7 of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN

- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. << For studies using a central laboratory add: This includes deciding which the tests available in the Hy's law lab kit should be used>>

- Complete the 3 Liver CRF Modules as information becomes available

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to patients << with liver metastases>> who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required
  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Potential Hy's Law Criteria met of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of

whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, eg, chronic or progressing malignant disease, severe infection or liver disease, << or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment >>?

If No: follow the process described in Potential Hy's Law Criteria met of this Appendix

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix D Anaphylaxis: signs and symptoms, management

1. INTRODUCTION

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

If an anaphylactic reaction occurs, a blood sample will be drawn from the patient as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge for analysis of serum tryptase.

2. CLINICAL CRITERIA FOR DEFINING ANAPHYLAXIS AND IMMUNE COMPLEX DISEASE

Anaphylaxis

In adults, anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

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

AND AT LEAST 1 OF THE FOLLOWING

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

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

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

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

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

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

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

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

Immune Complex Disease

Immune complex disease or Hypersensitivity Type III is evoked by the deposition of antigenantibody 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. SIGNS AND SYMPTOMS AND MANAGEMENT OF ACUTE ANAPHYLAXIS

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

- Diffuse erythema

- Pruritus

- Urticaria and/or angioedema

- Bronchospasm

- Laryngeal edema

- Hypotension

- Cardiac arrhythmias

- Feeling of impending doom

- Unconsciousness

- Shock

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles

- Rhinorrhea

- Change in voice

- Metallic taste

- Nausea, vomiting, diarrhea, abdominal cramps and bloating

- Lightheadedness

- Headache

- Uterine cramps

- Generalized warmth

4. MANAGEMENT OF ACUTE ANAPHYLAXIS

4.1 Immediate intervention

1. Assessment of airway, breathing, circulation, and adequacy of mentation

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

4.2 Possibly appropriate, subsequent measures depending on response to epinephrine

(a) Place patient in recumbent position and elevate lower extremities.

(b) Establish and maintain airway.

(c) Administer oxygen.

(d) Establish venous access.

(e) Normal saline IV for fluid replacement.

4.3 Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion.

(b) Consider H1 and H2 antihistamines.

(c) Consider nebulized β2 agonist [eg, albuterol (salbutamol)] for bronchospasm resistant to epinephrine.

(d) Consider systemic corticosteroids.

(e) Consider vasopressor (eg dopamine).

(f) Consider glucagon for patient taking b-blocker.

(g) Consider atropine for symptomatic bradycardia.

(h) Consider transportation to an emergency department or an intensive care facility.

(i) For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary.

Adapted from: Kemp SF, Lockey RF, Simons FE; World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephr

5. REFERENCES

Johansson et al 2004
Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004; 113(5): 832-6.

Appendix E PROHIBITED AND RESTRICTED MEDICATIONS

Asthma medication restrictions

Table 1 Asthma medications restrictions

Medication	Prohibited/restricted	Details
Long-acting beta-agonists as a reliever (eg, Symbicort Maintenance and Reliever Treatment)	Prohibited	Not allowed from enrolment and throughout the study duration
Zileuton	Prohibited	Not allowed 30 days prior to Visit 1; during treatment period

Other medication restrictions

Table 2 Other medication restrictions

Medication	Prohibited/restricted	Details
Live Attenuated Vaccines	Prohibited	Not allowed 30 days prior to randomization; during treatment period, and 16 weeks (5 half-lives) after the last dose of the investigational product
Inactive/killed vaccinations (eg, inactive influenza)	Restricted	Not allowed within the 7 days before or within the 7 days after any study visit
Any immunomodulators or immunosuppressives	Prohibited	Not allowed within 3 months prior to the date informed consent is obtained.; during treatment period; 3 Months or 5 Half Lives (whichever is longer) after Last Dose
Any immunomodulators or immunosuppressives – topical	Restricted	Topical administration of Immunosuppressive medication may be allowed at the discretion of the Investigator after discussion with the AstraZeneca Study Physician
Blood products or immunoglobulin therapy	Prohibited	Not allowed 30 days prior to date of ICF; during treatment period

Table 2 Other medication restrictions

Medication	Prohibited/restricted	Details
Any marketed (eg, Omalizumab, mepolizumab) or investigational biologic treatment	Prohibited	Not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1; during treatment period; 4 months or 5 half-lives (whichever is longer) after the last dose of the investigational product
Other investigational Products	Prohibited	Not allowed 30 Days or 5 Half Lives (whichever is longer) prior to Visit 1; during treatment period
Allergen Immunotherapy	Restricted	Allowed if on stable therapy for at least 30 days prior to date of ICF; no anticipated changed during treatment
Herbal remedies for the treatment of allergic, inflammatory, or respiratory	Prohibited	Not allowed 30 days prior to Visit 1 or during the treatment period
Roflumilast	Prohibited	Not allowed 30 days prior to Visit 1 and during the treatment period
Oral or ophthalmic β-adrenergic antagonist (eg, propranolol)	Prohibited	Patients currently using any oral or ophthalmic β-adrenergic antagonist at the time of enrolment are not eligible for the study. Not allowed during treatment period

Appendix F BACKROUND THERAPY EQUIVALENCE TABLE

Table 1 Estimated daily dosage for inhaled corticosteroids

Asthma therapy: Inhaled corticosteroid	Total daily dose (µg/day)	
	Medium	High
Beclomethasone dipropionate	>500 - 1000	>1000
Beclomethasone HFA	>200 - 400	>400
Beclomethasone dipropionate (Fostair)	>200 - 400	>400
Ciclesonide	>160 - 320	>320
Triamcinolone acetonide	>1000 - 2000	>2000
Flunisolide	>1000 - 2000	>2000
Fluticasone propionate	>250 - 500	>500
Fluticasone propionate HFA	>250 - 500	>500
Budesonide	>400 to 800	>800
Budesonide, if as delivered dose (eg, Symbicort)	>320 to <640	≥640
Mometasone furoate	>220 - 440	>440

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Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.