AstraZeneca

Clinical Study Protocol	
Drug Substance	Benralizumab (MEDI-563)
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A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Adult Patients with Mild to Moderate Persistent Asthma

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	**Date of Amendment**	**Local Amendment No:**	**Date of Local Amendment**

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

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.

PROTOCOL SYNOPSIS

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Adult Patients with Mild to Moderate Persistent Asthma

International Coordinating Investigator

Gary T. Ferguson, M.D., P.C.

Study center(s) and number of patients planned

This study will be conducted worldwide in approximately 80 study centers. Target is to randomize 200 patients.

Study period		Phase of development
Estimated date of first patient enrolled	Q1 2015	Phase 3
Estimated date of last patient completed	Q1 2016	

Objectives

(a) Primary Objective

Objective	Endpoint
To evaluate the effect of benralizumab on pulmonary function in mild to moderate asthmatic patients	• Change from baseline in pre-dose FEV_1 at Week 12

(b) Secondary Objectives

Objective	Endpoint
To assess the effect of benralizumab on asthma symptoms and other asthma control metrics	• Change from baseline in morning and evening peak expiratory flow at home at Week 12 • Change from baseline in total asthma symptom score at Week 12 • Change from baseline in total asthma rescue medication use (average puffs/day) at Week 12 • Change from baseline in nighttime awakening due to asthma and requiring rescue medication at Week 12 • Change from baseline in mean Asthma Control Questionnaire-6 (ACQ-6) score at Week 12 • Asthma exacerbations
To assess the effect of benralizumab on asthma related and general health-related quality of life	• Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(S)+12) total and domain scores at Week 12
To evaluate the pharmacokinetics, pharmacodynamics, and immunogenicity of benralizumab	• Pharmacokinetic parameters • Peripheral blood eosinophil levels • Anti-drug antibodies

(c) Safety Objective

Objective	Endpoint
To assess the safety and tolerability of benralizumab	• Adverse events (AEs) and serious adverse events (SAEs) • Laboratory variables • Physical Examination

Study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate the efficacy and safety of a fixed 30 mg dose of benralizumab administered subcutaneously (SC) in patients with mild to moderate persistent asthma. Approximately 200 patients will be randomized globally to receive 3 SC doses (Week 0, Week 4, and Week 8) of benralizumab 30 mg or placebo.

After enrollment, eligible patients will enter a 2 to 4 week screening/run-in period, at which time all patients, irrespective of their previous background therapy, will be converted to either 180 or 200 μg dry powder inhaler twice daily (based on what is approved in the country where the study site is located) for the duration of the study.

Patients who continue to meet eligibility criteria will be randomized on Week 0 to receive 3 SC doses (Week 0, Week 4, and Week 8) of benralizumab 30 mg or placebo, with an end of treatment (EOT) visit at Week 12. Follow-up visits will be conducted at Week 16 (FU1) and Week 20 (FU2).

Target patient population

Male and female adult patients 18 to 75 years of age, inclusive, with mild to moderate persistent asthma will be enrolled.

Investigational product, dosage and mode of administration

Benralizumab 30 mg/mL solution for injection in an accessorized pre-filled syringe (PFS) will be administered at the study center SC every 4 weeks for 3 doses (Week 0, Week 4, and Week 8).

Comparator, dosage and mode of administration

Matching placebo solution for injection in an accessorized PFS will be administered at the study center SC every 4 weeks for 3 doses (Week 0, Week 4, and Week 8).

Duration of treatment

Following enrollment, the patient will enter a 2 to4 week screening/run-in period followed by a 12-week double-blind, randomized treatment period, with the last dose of benralizumab/placebo administered at Week 8. The EOT visit will be conducted on Week 12. Follow-up visits will be conducted at Week 16 and Week 20.

The total planned study duration is a maximum of 24 weeks.

Statistical methods

Patients will be stratified by blood eosinophil count (<300 or ≥300 cells/μL) and region, the approximately 200 patients will be randomized to SC benralizumab 30 mg or placebo in a 1:1 ratio. The stratification will be done to remove potential confounding effects of geographic region and eosinophil levels on treatment effect. The study is powered for the primary efficacy endpoint analysis of change from baseline in pre-bronchodilator (pre-BD) FEV_1 at Week 12. Assuming a standard deviation of 350 mL and a two-sided 5% level t-test, the study has 80% power to detect a true treatment difference (benralizumab – placebo) of 140 mL and 90% power to detect a true treatment difference of 162 mL. Based on the assumptions above, the minimum difference that would be statistically significant at the 5% level is 98 mL.

Change from baseline in pre-BD FEV_1 at Week 12 will be compared between the benralizumab treatment group and placebo using a repeated measures analysis. Treatment group will be fitted as the explanatory variable, and eosinophil level (<300 or ≥300 cells/μL), region, and baseline pre-BD FEV_1 will be fitted as covariates. Visit will be fitted as a categorical variable. The full analysis set includes all randomized patients who received any dose of investigational product, irrespective of their protocol adherence and continued participation in the study.

All safety parameters will be summarized descriptively. Safety analyses will be based on the safety analysis set, defined as all patients who received at least 1 dose of any investigational product.

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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.

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
ANCOVA	Analysis of covariance
AQLQ(S)+12	Standardized Asthma Quality of Life Questionnaire for 12 Years and Older
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
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency department
EOT	End of treatment
ePRO	Electronic patient reported outcome
EU	European Union
EXACA	Exacerbation eCRF
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
Gamma-GT	Gamma-glutamyl transpeptidase

Abbreviation or special term	Explanation
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
GLI	The Global Lung Function Initiative
HCP	Health care provider
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
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
IP	Investigational product
IPD	Premature IP Discontinuation
IRB	Institutional Review Board
ISF	Investigator Study File
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
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
PN	Predicted normal
Post-BD	Post-bronchodilator
Pre-BD	Pre-bronchodilator

Abbreviation or special term	Explanation
PRO	Patient reported outcome
RBC	Red blood cell
SABA	Short-acting β_2 agonists
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SUSARs	Suspected Unexpected Serious Adverse Reactions
ULN	Upper limit of normal
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 β_2 agonists (LABA) in patients with more severe asthma (GINA 2011, NAEPP 2007). Despite treatment per management guidelines, up to 50% of patients have asthma that is not well controlled (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, Simpson et al 2006, Zhang and Wenzel 2007).

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 the IL-5 pathway 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 2012). 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, Gossage et al 2012, Molfino et al 2012). 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. Two regimens are being studied relative to placebo, those being either 30 mg every 4 weeks (Q4W) or 30 mg every 4 weeks for the first 3 doses followed by every 8 weeks (Q8W) thereafter. These regimens were chosen to allow for a direct determination of the immunogenicity profile of benralizumab on efficacy and safety, if any. The 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.

As discussed, benralizumab is in Phase 3 trials in patients with severe asthma. However, it is important to consider the use of benralizumab across a fuller range of asthma severity. As such the purpose of this trial is to investigate the efficacy and safety of benralizumab in adult patients with mild to moderate persistent asthma.

1.2 Rationale for study design, doses and control groups

This is a global study designed to investigate the safety and efficacy of the fixed dose benralizumab (30 mg) administered subcutaneously (SC) every 4 weeks (at Week 0, Week 4, and Week 8) in patients with mild to moderate persistent asthma.

Primary efficacy will be determined based on change from baseline in forced expiratory volume in 1 second (FEV_1) at Week 12. The Phase 2b Study demonstrated benefit as early as 4 weeks after the first dose and a plateau effect was reached by Week 8; therefore, the Sponsor believes that 12 weeks is sufficient in duration for the study.

The benralizumab dose (30 mg SC, fixed) is based on all available safety, efficacy, and immunogenicity data, as well as population exposure-response modeling, and stochastic trial simulations from earlier phase benralizumab trials. Other stable asthma therapies on top of inhaled corticosteroids/long-acting β_2 agonists (ICS/LABA) that are within expert guidance and that are not restricted per protocol (see Section 3.5.2) are allowed in order to accommodate local standards of care.

1.3 Benefit/risk and ethical assessment

Benralizumab is principally being studied in severe asthmatics where there are few treatment options for patients whose asthma remains uncontrolled on high dose ICS/LABA and oral corticosteroids (GINA 2011). 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), risks that have not been seen to date. Also, 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 purpose of this trial, however, is to confirm the safety and clinical benefit of benralizumab administration in asthma patients with mild to moderate persistent asthma in order for us to gain an understanding of the benefit/risk of benralizumab across the spectrum of asthma disease. A more detailed assessment of the overall risk/benefit of benralizumab in patients with asthma is given in the Investigator's Brochure.

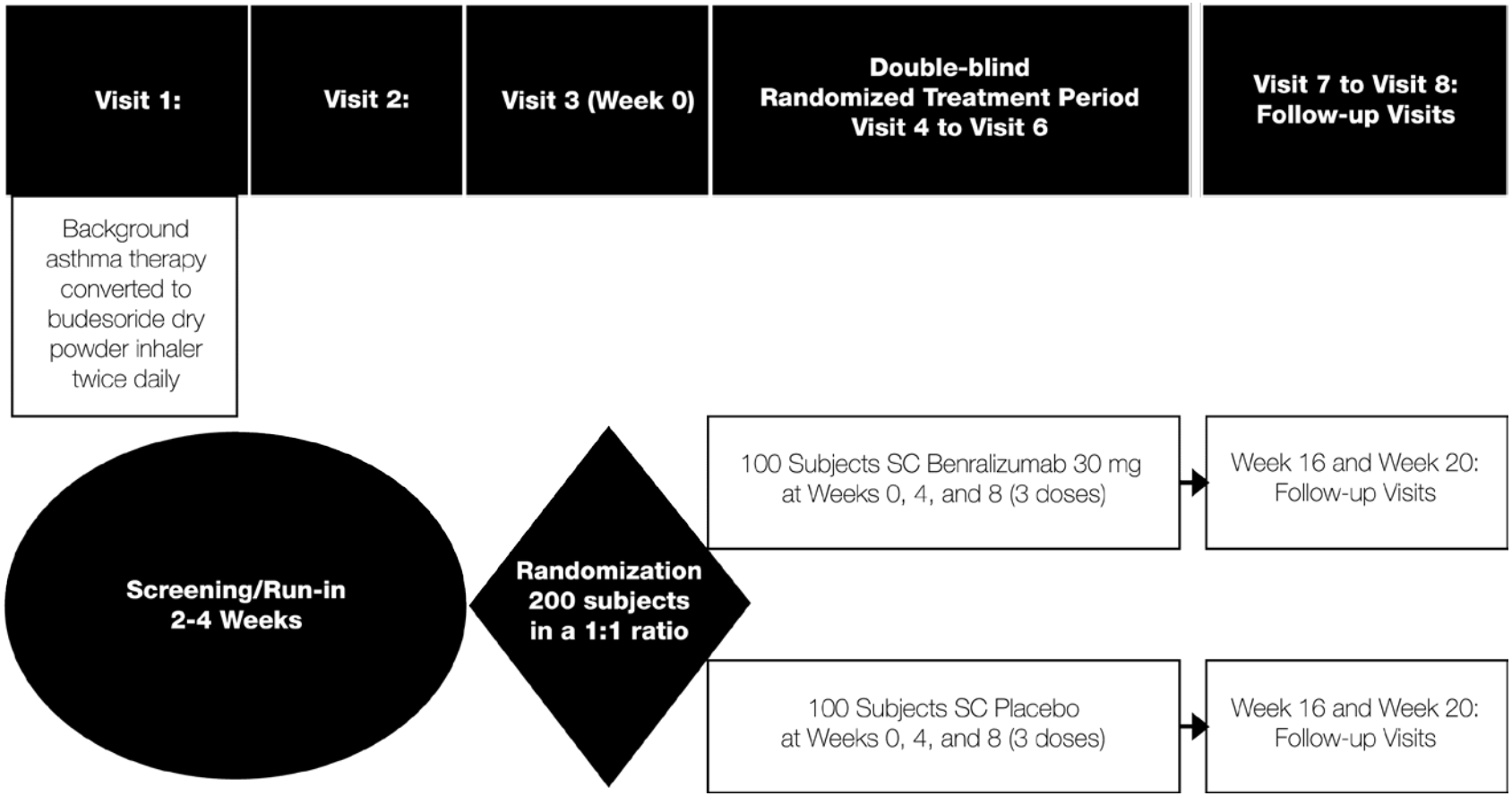
1.4 Study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate the efficacy and safety of a fixed 30 mg dose of benralizumab administered SC in patients with mild to moderate persistent asthma. Approximately 200 patients will be randomized globally to receive SC benralizumab 30 mg or placebo administered at Week 0, Week 4, and Week 8.

After enrollment, eligible patients will enter a 2 to 4 week screening/run-in period, at which time all patients, irrespective of their previous background therapy, will be converted to either 180 or 200 μg of budesonide dry powder inhaler twice daily (based on what is approved in the country where the study site is located) for the duration of the study.

Patients who continue to meet eligibility criteria will be randomized on Week 0 to receive 3 SC doses (Week 0, Week 4, and Week 8) of benralizumab 30 mg or placebo, with an end of treatment (EOT) visit at Week 12. Follow-up visits will be conducted at Week 16 and Week 20 (Figure 1).

Figure 1 Study flow chart



2. STUDY OBJECTIVES

2.1 Primary Objective

Objective	Endpoint
To evaluate the effect of benralizumab on pulmonary function in mild to moderate asthmatic patients	• Change from baseline in pre-dose FEV_1 at Week 12

2.2 Secondary Objectives

Objective	Endpoint
To assess the effect of benralizumab on asthma symptoms and other asthma control metrics	• Change from baseline in morning and evening peak expiratory flow (PEF) at home at Week 12 • Change from baseline in total asthma symptom score at Week 12 • Change from baseline in total asthma rescue medication use (average puffs/day) at Week 12 • Change from baseline in nighttime awakening due to asthma and requiring rescue medication at Week 12 • Change from baseline in mean ACQ-6 score at Week 12 • Asthma exacerbations
To assess the effect of benralizumab on asthma related and general health-related quality of life	• Change from baseline in AQLQ(S)+12 total and domain scores at Week 12
To evaluate the pharmacokinetics, pharmacodynamics, and immunogenicity of benralizumab	• Pharmacokinetic parameters • Peripheral blood eosinophil levels • Anti-drug antibodies

2.3 Safety Objective

Objective	Endpoint
To assess the safety and tolerability of benralizumab	• Adverse events (AEs) and serious adverse events (SAEs) • Laboratory variables • Physical Examination

3. PATIENT SELECTION, ENROLLMENT, DISCONTUATION, AND WITHDRAWAL CRITERIA

3.1 Inclusion criteria

For inclusion in the study patients must fulfill all of 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. Women of childbearing potential (WOCBP) must use a highly effective form of birth control (confirmed by the Investigator). Highly effective forms of birth control includes: true sexual abstinence, a vasectomized sexual partner, , female sterilization by tubal occlusion, any effective IUD Intrauterine device/IUS Ievonorgestrel Intrauterine system, oral contraceptive, and or WOCBP must agree to use highly effective method of birth control, as defined above, from enrollment, 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 postemenopausal 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.

4. 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.

5. Weight of ≥40 kg

6. Evidence of asthma as documented by post-bronchodilator (post-BD) reversibility in FEV_1 of ≥ 12% demonstrated at Visit 2

7. Documented use of 1 of the following types of asthma therapy at time of informed consent:

   - Low- to medium-dose ICS (ie, 100 to 500 μg fluticasone dry powder formulation equivalents total daily dose) with or without other controller medications, eg, an LTRA and/or theophylline or

   - Low-dose ICS/LABA fixed combination therapy (eg, the lowest regular maintenance dose approved in the local country will meet this criterion)

8. Morning pre-bronchodilator (pre-BD) FEV_1 of > 50% to ≤ 90% predicted at Visit 2

Inclusion criteria at randomization

9. At least one of the following symptoms within 7 days prior to randomization:

   a. Daytime or nighttime asthma symptom score of ≥1 for more than or equal to 2 days;

   b. Rescue SABA use on at least 2 days; or

   c. Nighttime awakenings due to asthma at least 1 night during the 7-day period

10. For WOCBP: have a negative urine pregnancy test prior to administration of the IP

11. Demonstrate acceptable inhaler, peak flow meter, and spirometry techniques during screening

12. Complete symptom scores, PEF measurements and information relating to rescue medication use on 4 or more days out of the last 7 days immediately preceding Visit 3

3.2 Exclusion criteria

Patients must 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. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, 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

3. Known history of allergy or reaction to the investigational product formulation

4. History of anaphylaxis to any biologic therapy

5. History of Guillain-Barré syndrome

6. 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

7. 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

8. 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

9. 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

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

11. 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

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

13. Current smokers or former smokers with a smoking history of ≥10 pack years

14. History of cancer:

    - 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.

15. Use of immunosuppressive medication (including but not limited to: oral corticosteroid, methotrexate, troleandomycin, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid, or any experimental anti-inflammatory therapy) within 3 months prior to the date informed consent

16. Current use of an oral or ophthalmic non-selective β-adrenergic antagonist (eg, propranolol)

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

18. Five- lipoxygenase inhibitors (eg, Zileuton) and roflumilast are prohibited.

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) 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

- Receipt of inactive/killed vaccinations (eg, inactive influenza) is allowed provided they are not administered within 1 week before/after any investigational product administration.

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. Initiation of new allergen immunotherapy is not allowed within 30 days prior to the date of informed consent. Immunotherapy initiated prior to this period or as a routine part of the patient's seasonal treatment is allowed. If the immunotherapy is delivered as an injection, there should be a gap of 7 days between the immunotherapy and investigational product administration.

25. Planned surgical procedures during the conduct of the study

26. Currently breastfeeding or lactating women

27. Previous randomization in the present study

28. Concurrent enrollment in another clinical trial

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

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

31. 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.

Exclusion criteria at randomization

32. Absolute FEV_1 at randomization visit (Week 0) that changes by more than 20% (negative or positive) from the screening value

33. An upper respiratory tract infection in the 2 weeks before randomization visit (Week 0)

34. Use of oral corticosteroids during the screening/run-in period

35. Poorly controlled asthma during the screening/run-in period defined as hospitalization or an emergency room visit for the treatment of asthma

For procedures for withdrawal of incorrectly enrolled or randomized patients see Section 3.4.

3.3 Patient enrollment and randomization

Investigator(s) should keep a record of patients considered for and included in the study. This pre-screening/screening log will be evaluated periodically by AstraZeneca or its delegates during routine monitoring visits.

Each patient 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.

The Investigator will:

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

2. Assign each potential patient a unique enrollment number beginning with E# via interactive web/voice response system (IWRS/IVRS)

3. Determine patient eligibility

4. Assign eligible patient 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.

3.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not – under any circumstance – be enrolled 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.

3.5 Concomitant medications, restrictions during, and after the study

3.5.1 Concomitant medication

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 1 and Table 2) and recorded in the eCRF.

Note: To satisfy inclusion criterion 7 (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 (see Section 3.9.1).

3.5.1.1 Background medication

After enrollment, eligible patients will enter a 2 to 4 week screening/run-in period at which time all patients, irrespective of their previous background therapy, will be converted to either 180 or 200 μg of budesonide dry powder inhaler twice daily (depending on what is approved in the country where the study site is located) for the duration of the study.

The background medication budesonide will be provided by AstraZeneca according to local regulations in order to maintain appropriate oversight and access to this concomitant therapy.

3.5.1.2 Rescue medication

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

3.5.2 Restrictions

3.5.2.1 Asthma medication restrictions

(a) Use of SABA

Regularly scheduled SABA use in the absence of any asthma symptoms and/or planned exercise is discouraged from enrollment and throughout the study duration.

Prophylactic use of SABA in the absence of symptoms (eg, prior to planned exercise) is discouraged. However, if deemed necessary by the patient and Investigator, SABA use is permitted as needed for worsening asthma symptoms (ie, rescue use).

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

(c) **Use of long-acting beta-agonists** as a reliever (eg,) is not allowed from enrollment and throughout the study duration.

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

All patients will be maintained on either 180 or 200 μg of budesonide dry powder inhaler twice daily (based on what is approved in the country where the study site is located) from Visit 1 through Week 20 (Visit 8).

Changes to the patient's background controller regimen are discouraged during the study unless judged medically necessary by the Investigator; ideally such changes should be discussed with the AstraZeneca Study Physician. All changes in the patient's background medication should be documented in source along with rational for change and recorded in eCRF.

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

(e) Asthma medication restrictions on the days of scheduled spirometry visit

Pre- and/or post-dose spirometry assessments will be performed at the study center at scheduled visits (see Table 1 and Table 2) restrictions to patient's background medication are required prior to the spirometry as described below (also see Section 4.1.1).

Screening/run-in Visit 2: SABAs should be withheld for 6 or more hours before spirometry.

If a patient fails the protocol-specified reversibility criterion (12% FEV_1) or FEV_1 criterion (>50% to ≤90%), a second attempt is allowed. Re-test can be done only once

during the screening period, not earlier than next calendar day and not later than 7 calendar days after the failed attempt.

Visits 3 to6: SABAs should be withheld for 6 or more hours for spirometry testing at each study visit. 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) or return on another day within the visit window.

(f) Asthma medication restrictions prior to home peak expiratory flow testing

Patients should avoid taking their rescue use medication and asthma controllers prior to the morning and evening peak flow (PEF) testing.

3.5.2.2 Other medication restrictions

(a) Use of immunosuppressive medication or administration of live/attenuated vaccines is not allowed. Topical administration of immunosuppressive medication may be allowed at the discretion of the Investigator after discussion with the AstraZeneca Study Physician. Refer to Section 3.2 exclusion criterion 15 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

(c) Patient should not receive allergen immunotherapy injection(s) within 7 days of IP administration

(d) When enrolling a patient who is on theophylline or digoxin, the Investigator should ensure the levels of each of these medications must not exceed the upper limit of therapeutic range. The Investigator will also be responsible for ensuring that these levels are regularly checked and documented as per local practice (see Table 1and Table 2)

(e) Patients should not take any other excluded medications:

- Five-lipoxygenase inhibitors (eg, Zileuton)
- Roflumilast
- Oral or ophthalmic non-selective β-adrenergic antagonist (eg, propranolol)

3.5.2.3 Other restrictions

(a) Fertile and sexually active patients or their partners should use highly 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 Section 3.1, inclusion criteria 3 and 4; and Section 6.3.2)

(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.

3.6 Discontinuation from investigational product

Patients will be discontinued from investigational product in the following situations:

1. Patient decision. The patient is free to discontinue treatment at any time, without prejudice (see Section 3.7)

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

3. Risk to patient as judged by the Investigator or AstraZeneca

4. Eligibility requirement found not to be fulfilled (see Section 3.4). Risk to patient as judged by the Investigator or AstraZeneca.

5. Pregnancy

6. Lost to follow-up[1]

7. Development of any study specific criteria for discontinuation:

    (a) Anaphylactic reaction to the investigational product requiring administration of epinephrine

    (b) Development of helminth parasitic infestations requiring hospitalization

    (c) An asthma-related event requiring mechanical ventilation

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. At that visit, patients should be encouraged to remain in the study to complete all subsequent study visits, procedures, and assessments, or alternatively, agree to be contacted by phone calls in order to collect AEs/SAEs, changes in concomitant medication, and

[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 one registered letter/certified mail; or one unsuccessful effort to check the vital status of the patient using publicly available sources, if allowed by local regulations.

asthma exacerbation information. Note that in this case, the IPD visit replaces the nearest regular visit (Visit 4 or Visit 5), while the following visits continue, as possible.

Patients not willing to continue to participate in the study should return to the study center 1 last time at 12 weeks (±3 days) after the last dose of IP for a final study-related assessment.

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

3.7 Withdrawal from the study

3.7.1 Screen failures

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

3.7.2 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 AE. The Investigator will follow up AEs outside of the clinical study. The patient will return electronic patient-reported outcome (ePRO) devices. The enrollment/randomization code of the withdrawn patient cannot be reused.

3.8 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of blood samples, the samples will be disposed of/destroyed and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator or designee:

- Ensures the local laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed.
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study center.

STUDY PLAN AND PROCEDURES

Table 1 Study Plan – Enrollment, screening/run-in period

Assessment/ activity	Refer to	Screening	
		V1	V2[a]
		(W -4 to W -2)	
Informed consent	9.4	X	
Inclusion/exclusion criteria	3.1/3.2	X	X
Medical and asthma history	3.9.1	X	
Complete physical examination	4.2.1.1	X	
Weight, Height, BMI	4.3.1	X	
Vital Signs	4.2.2	X	X
Central ECG	4.2.3	X	
Serum chemistry	4.2.4	X	
Hematology	4.2.4	X	
Urinalysis	4.2.4	X	
Serum concentration (digoxin, theophylline) [b]	3.5.2.2	X	
Serology (hepatitis B,C; HIV-1; HIV-2)	4.3.4.1	X	
Serum pregnancy test	4.2.4.1	X	
FSH [c]	4.2.4.1	X	
Screening reversibility [d]	4.1.1.1		X
PEF Testing	4.1.2		X
Asthma Daily Diary Instruction	4.3.2.1		X
Adverse events	6.1	X	X
Dispense budesonide	3.5.1.1	X	
Concomitant medication	3.5	X	X

[a] Visit 2 may take place as soon as medication restrictions prior to reversibility testing are met (see Section 3.5.2.1), and could occur at same time as Visit 1. **There must be at least 2 weeks between Visit 2 and Visit 3**.

[b] If and when appropriate prior to randomization; for patients who are on theophylline, digoxin, or other drugs with a narrow therapeutic range (see Section 3.5.2.2)

[c] FSH test done only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for ≥12 month

[d] The screening reversibility test is to be performed on Visit 2. If a patient fails the protocol-specified reversibility criterion (≥12% FEV_1) or FEV_1 criterion (>50% to ≤90%), a second attempt is allowed. Re-test can be done only once during the screening period, not earlier than next calendar day and not later than 7 calendar days after the failed attempt.

BMI Body mass index; D Days; ECG Electrocardiogram; FSH Follicle-stimulating hormone; HIV Human immunodefieciency virus; PEF Peak expiratory flow; V Visit; W Week.

Table 2 Study Plan – Randomization, treatment period, and follow-up

Assessment/ activity	Refer to	Treatment			EOT	IPD	FU1	FU2	Unsch
		V3	V4	V5	V6		V7	V8	
		W0	W4	W8	W12		W16	W20	
			Visit window (days) [a]						
		±0	±3	±3	±3	±3	±3	±3	
Inclusion/exclusion criteria	3.1/3.2	X							
Complete physical examination	4.2.1.1	X			X	X		X	
Brief physical examination	4.2.1.2		X	X			X		X
Vital Signs	4.2.2	X	X	X	X	X	X	X	X
Central ECG	4.2.3	X			X	X			
Serum chemistry [b]	4.2.4	X			X	X		X	
Hematology	4.2.4	X			X	X		X	
Urinalysis	4.2.4	X			X	X		X	
Urine pregnancy test (dipstick) [c]	4.2.4.1	X	X	X	X	X	X	X	
PK	4.3.5	X			X	X		X	
ADA/nAb [d]	4.3.7	X			X	X		X	
PEF and Asthma Daily Diary Adherence	4.1.2/4.3.2.1	X	X	X	X	X			
ACQ-6	4.3.2.2	X	X	X	X	X			
AQLQ (S) +12	4.3.2.3	X			X	X			
Health care resource utilization	4.3.3	X	X	X	X	X	X	X	
Pre- BD, spirometry	4.1.1	X	X	X	X	X			
Reversibility	4.1.1.1				X	X			

Table 2 Study Plan – Randomization, treatment period, and follow-up

Assessment/ activity	Refer to	Treatment			EOT	IPD	FU1	FU2	Unsch
		V3	V4	V5	V6		V7	V8	
		W0	W4	W8	W12		W16	W20	
			Visit window (days) [a]						
		±0	±3	±3	±3	±3	±3	±3	
Asthma exacerbation assessment	4.1.3	X	X	X	X	X	X	X	X
Dispense budesonide	3.5.1.1	X	X	X	X	X	X		
Adverse events	6.1	X	X	X	X	X	X	X	X
Concomitant medication	3.5	X	X	X	X	X	X	X	X
Randomization	3.3	X							
Administration of investigational product[e]	5.8	X	X	X					

[a] All visits are to be scheduled from the date of randomization, not from the date of previous visit, except in the case of early discontinuation from IP (see Section 3.6 for details).

[b] Detailed schedule for serum chemistry tests provided in Section 4.2.4, Table 3

[c] For WOCBP only, urine HCG test to be done at center on each study visit (before IP administration on V3-5)

[d] Neutralizing antibody (nAb) testing will occur for all samples that are ADA positive. Samples that are ADA negative will not be tested for nAb.

[e]

ACQ-6 Asthma Control Questionnaire 6; ADA Anti-drug antibodies; AQLQ (S)+12 Standardized Asthma Quality of Life Questionnaire for 12 Years and Older; BMI Body mass index; D Days; ECG Electrocardiogram; EOT End-of-treatment; FHS Follicle-stimulating hormone; FU Follow-up; HIV Human immunodeficiency virus; IPD Premature investigational product discontinuation; nAb Neutralizing antibodies; PEF Peak expiratory flow; Pre-BD Pre-bronchodilator; PK Pharmacokinetics; UNSCH Unscheduled; V Visit; W Week

3.9 Enrollment and screening/run-in period

3.9.1 Enrollment (Visit 1)

Each potential patient will provide written informed consent prior to any study specific procedures and undergo assessments applicable for the visit (see Table 1).

Patient must sign the Informed Consent Form (ICF) prior to any Visit 1 procedures and prior to instructing the patient to withhold any medication. Registration of patient's enrollment via IWRS/IVRS should occur on day when other Visit 1 procedures are done.

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. A patient's verbal history suggestive of asthma symptoms, but without supporting documentation, is not sufficient to satisfy these inclusion criteria.

Current, regular use of ICS prior to enrollment must be documented in the source. This documentation may be in the form of a recent, active medication list as per a health care provider (HCP) note, or filled prescriptions based on a pharmacy record.

At the time of screening/run-in, all patients, irrespective of their previous background therapy, will be converted to twice daily budesonide dry powder inhaler for the duration of the study.

3.9.2 Screening/run-in (Visit 2)

The screening/run-in period should be a minimum of 2 weeks in duration. Assessments applicable for the period are listed in Table 1.

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

Visit 2 may take place as soon as medication restrictions prior to spirometry/reversibility tests are met (see Section 3.5.2.1), and should occur no later than 1 week after Visit 1. Visit 2 spirometry/reversibility procedures may be performed on the same day as Visit 1 if the medication restriction is met.

If a patient fails the protocol-specified reversibility criterion ($\geq$12% FEV_1) or FEV_1 (> 50% to $\leq$ 90%) criteria, a second attempt is allowed. Re-testing can only occur once during the run-in period, not earlier than next calendar day and not later than 7 calendar days after the failed attempt.

Once the reversibility criterion has been met, the patient will be supplied with an electronic peak flow meter to monitor home lung function, and an ePRO device to record asthma symptoms and complete relevant questionnaires (see Section 4.3.2 for further details).

3.9.3 Re-screening

Re-screening is allowed only once for the patient.

Patients with respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date of informed consent or during the screening/run-in period may be re-screened if the upper respiratory tract infection is not within 2 weeks before the randomization visit (see Section 3.2, exclusion criterion 33).

If the reason for screen failure was transient (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits), patients may potentially be re-screened. These cases should be discussed with the AstraZeneca Monitor and documented in the Investigator Study File (ISF).

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

3.9.3.1 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 and will be considered a screen failure.

3.10 Randomized treatment period

Inclusion criteria at randomization will be confirmed at Week 0. The patient's compliance with ePRO completion must be confirmed before randomization (see Section 3.1, inclusion criterion 12).

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

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

During the Week 0 visit, but before the first dose of IP, the patient should complete the following assessments: AQLQ(S)+12 and ACQ-6.

For Visits 3 to5, spirometry and blood sampling may be performed 1 day prior to the scheduled date of IP injection, at the discretion of the Investigator. All other study procedures must be done on the scheduled day of IP injection. Urine pregnancy tests must be done on injection days, prior to IP administration. Following randomization, the patient will receive treatment with IP on Week 0, Week 4, and Week 8.

Patients will have scheduled visits at 4-week intervals to complete protocol-specific assessments and IP administration as listed in Table 2. Restrictions as set out in Section 3.5.2 will continue to apply throughout the treatment period. In case of an asthma worsening/exacerbation (see Section 4.1.3), patients should be evaluated at the study center, when feasible.

Patients will continue to monitor lung function at home, as well as record asthma symptoms using ePRO device through the EOT visit (see Section 4.3.2 for details).

At Week 12 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 3.6.

Patients will return the ePRO device on EOT visit.

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

3.11 Follow-up period

Patients who complete the double-blind randomized treatment period will have follow-up visits at Weeks 16 and 20.

4. STUDY ASSESSMENTS AND TIMING OF PROCEDURES

4.1 Efficacy assessments

4.1.1 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 Visits 2 through 6 (see Section3.5.2.1). If Visits 1 and 2 are combined, LABA therapy (with or without ICS) should be withheld for 12-24 hours depending on whether the patient is using twice- or once-daily LABA-containing therapy.

Options for handling patients who have inadvertently taken their asthma medication within the restricted window are described in Section 3.5.2.

Time of day for scheduled center visit spirometry

Spirometry testing should be done according to the schedule provided in Table 1 and Table 2. All post-randomization spirometry assessments should be performed within ±1.5 hours of the

time that the randomization spirometry was performed. For example, if the randomization spirometry was started at 8:00 AM, then all subsequent spirometry testing needs to be initiated between 6:30 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 enrollment 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).

Post-bronchodilator spirometry

Post-BD spirometry will be performed to satisfy reversibility inclusion criterion 6. The post-BD spirometry procedure should commence within 30±15 minutes according to the regimen for reversibility testing outlined in Section 4.1.1.1.

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 initial pre-medication, pre-BD spirograms are complete for the reasons discussed above; usual asthma controller may be given after l post-BD spirograms for all visits except in the case of the screening and EOT visits, where they may be given after the post-BD spirogram. Investigational product dosing should also be withheld 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, enrollment 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% of PN = FEV_1 measured/FEV_{1PN} x 100

4.1.1.1 Reversibility test

The procedure described in this section refers to the reversibility testing at Visit 2 (to evaluate inclusion criterion 6 if applicable) and at V6. Bronchodilatation should be induced using 4 puffs of albuterol (90 µg metered dose), salbutamol (100 µg metered dose), or levalbuterol (45 µg metered dose) (Sorkness et al 2008). It is highly recommended to use a spacer device for this procedure. A nebulizer should not be used.

4.1.2 Home Peak Expiratory Flow testing

An electronic peak flow meter will be dispensed to the patient on Visit 2 (after respiratory inclusion criteria have been confirmed, see Section 3.1, criteria 6 and 8).

Home peak expiratory flow (PEF) testing will be performed by the patient in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Recording of home lung function should start from the evening of Visit 2 until the morning of Visit 6 (Week 12) using an ePRO device. When possible, ambulatory lung function measurements should be taken at least 6 hours after the last dose of SABA rescue medication.

Patients should perform 3 successive peak flow maneuvers while sitting or standing, but in the same position at every testing; the highest of the 3 values will be captured for the morning and for the evening maneuvers.

The Investigator/authorized delegate will check patient's adherence to correct use of the peak flow meter at each visit as shown in Table 2.

4.1.3 Assessment of asthma exacerbations

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

- Use of systemic corticosteroids for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids

- An emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care center) due to asthma that required systemic corticosteroids (as per above)
- An inpatient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma

4.2 Safety assessments

4.2.1 Physical examination

Physical examination will be done in accordance with the schedules provided in Table 1 and Table 2.

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 6.1.

4.2.1.1 Complete physical examination

The complete physical examination includes an assessment of the following: general appearance, skin, head and neck (including eyes, ears, nose, mouth, and throat), lymph nodes, abdomen, musculoskeletal (including spine and extremities), cardiovascular, respiratory, and neurological systems.

4.2.1.2 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.

4.2.2 Vital signs

Pre-dose vital signs (pulse, blood pressure, respiration rate, and body temperature) are to be obtained in accordance with schedule provided in Table 1 and Table 2.

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.

Body temperature is to be recorded in degrees Celsius.

4.2.3 Central ECG

ECG are to be performed in accordance with the schedule provided in Table 1 and Table 2. The equipment will be provided by a central vendor, and only this equipment should be used for assessment throughout the patient's participation in the study.

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).

A standard ECG with a recommended paper speed of 50 mm/second covering at least 6 sequential beats will be used. 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. The ECG will be transmitted to a central reader.

ECG data and evaluation will be recorded in the eCRF.

4.2.4 Safety laboratory tests

Safety laboratory tests (list provided in Table 3) will be performed in a central laboratory. For information on methods of collection, assessment, labeling, 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 1 and Table 2.

Hematology and urinalysis will be assessed in line with the schedules provided in Table 1 and Table 2.

Laboratory results should be reviewed by the Investigator/authorized delegate and evaluated for abnormalities. Any laboratory abnormalities considered to be significant in the Investigators'/authorized delegate's judgment should be reported as described in Section 6.1.3.

The copy of laboratory result report should be signed and dated by the Investigator and retained at the study center.

Table 3 List of safety laboratory tests

Serum chemistry		Hematology	Urinalysis
Alkaline phosphatase	Gamma-GT (gamma-glutamyl transpeptidase)	Hematocrit	Appearance
ALT (alanine aminotransferase)	Glucose	Hemoglobin	Blood
AST (aspartate aminotransferase)	Phosphorus	Mean corpuscular volume (MCV)	Color
BUN (blood urea nitrogen)	Potassium	Platelet count	Glucose
Calcium	Sodium	Red blood cell (RBC) count	Ketones

Chloride	Total bilirubin	White blood cell (WBC) count with differential[a]	Microscopy including WBC/high power field (HPF), RBC/HPF
CO_2 (carbon dioxide)	Total cholesterol		pH
Creatinine	Uric acid		Specific gravity
Serum concentration [b]			

[a] Eosinophil, basophil and monocyte counts will be redacted from the central laboratory reports, except for Visit 1 (see Section 5.6).
[b] For patients on theophylline or digoxin, see Section 3.5.2.2.

4.2.4.1 Pregnancy test

The following tests are applicable to female patients only and will be conducted in accordance with the schedules provided in Table 1 and Table 2:

- Serum beta-hCG: To be done at screening Visit 1 only, 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 V3-5) using a dipstick. A positive urine test result must be confirmed with serum beta HCG.

4.3 Other assessments and procedures

4.3.1 Weight and height

Weight and height will be measured, and BMI calculated in accordance with schedules provided in Table 1.

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.

4.3.2 Patient reported outcomes

Patients will be supplied with an ePRO device and peak flow meter at Visit 2 after respiratory criteria have been confirmed (see Section 3.1, inclusion criteria 6 and 8). The study center staff will be trained on how to use both devices and will be responsible for instructing patients on how to use both devices. Patients will have an opportunity to practice using the devices through a pre-programmed training module. Patients should be informed that the recordings made electronically cannot be retrospectively or prospectively entered and must be completed within a defined time window. Patients will also be provided with information about when and where to request help if problems occur.

4.3.2.1 Asthma Daily Diary

The Asthma Daily Diary will be completed each day from the evening of Visit 2 to the morning of Visit 6. The Asthma Daily Diary will include the following daily recordings: morning and evening home lung function data (obtained from the home peak flow meter), asthma symptoms, inhalations of rescue medication, and nights with awakenings due to asthma symptoms. The Investigator/authorized delegate will check patient's adherence to the Asthma Daily Diary at each visit as shown in Table 2.

Home peak expiratory flow measurement

For details regarding home lung function measurement, refer to Section 4.1.2.

Asthma symptom score

Asthma symptoms during nighttime and daytime will be recorded by the patient each morning and evening in the Asthma Daily Diary. Symptoms will be recorded using a scale of 0-3, where 0 indicates no asthma symptoms. Asthma symptom daytime score (recorded in the evening), nighttime score (recorded in the morning), and total score will be calculated and presented separately. The daily asthma symptom total score will be calculated by taking the sum of the nighttime and daytime asthma symptom scores recorded each day. If a patient is missing a value for either nighttime or daytime asthma symptom score on a given day, then the total score for that day will be set to missing.

The secondary outcome variable is the weekly mean daily asthma symptom total score. Weekly means for daytime and nighttime scores will also be calculated.

Rescue medication

The number of rescue medication inhalations and nebulizer treatments taken will be recorded by the patient in the Asthma Daily Diary twice daily. The number taken between the morning and evening lung function assessments will be recorded in the evening. The number of inhalations taken between the evening and morning lung function assessments will be recorded in the morning. Rescue medication usage is captured in the daily diary as the number of inhaler puffs and the number of times a nebulizer is used. Rescue medication usage will be summarized as the number of puffs with 1 instance of nebulizer use converted to 2 puffs.

Nighttime awakenings

Nighttime awakenings due to asthma symptoms will be recorded by the patient in the Asthma Daily Diary each morning by answering the question whether he/she woke up during the night due to asthma symptoms by a "yes" or "no" response.

4.3.2.2 Asthma Control Questionnaire (ACQ-6)

The ACQ-6 is a shortened version of the 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.

The questionnaire will be completed at the study center in accordance with schedule provided in Table 2.

4.3.2.3 Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12)

The AQLQ(S)+12 is a questionnaire that measures the health-related quality of life experienced by asthma patients.

The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli).

Patients are asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The 4 individual domain scores (symptoms, activity limitations, emotional function, and environmental stimuli) are the means of the responses to the questions in each of the domains. Individual AQLQ(s)+12 total or domain score changes of ≥0.5 are considered clinically meaningful.

The questionnaire will be completed at the study center in accordance with schedule provided in Table 2.

4.3.3 Health care resource utilization

Broad-based health care utilization asthma related event information will be collected by the Investigator/authorized delegate at each visit (as shown in Table 2) and recorded in the appropriate eCRF module.

At Visit 3 Healthcare Resource Utilization (HRU) information will be collected with a 1 year recall period. The subsequent visits will collect HRU information with a recall period of 'since last visit'.

Note: Cases of hospitalization also must be reported as an SAE (see Section 6.1.2 and 6.1.5).

4.3.4 Other screening/run-in assessments

4.3.4.1 Serology

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

HIV-1 and HIV-2 antibodies: To be done only at enrollment (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.

4.3.5 Pharmacokinetics

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 pre-dose at Visit 3, as well as at Visits 6 and 8, according to the study plan (see Table 2).

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

The PK samples will be retained at AstraZeneca or designee for a maximum of 15 years following Last Patient's Last Visit.

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

4.3.6 Pharmacodynamics

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]).

4.3.7 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 a designee for a maximum of 15 years following the Last Patient's Last Visit.

A summary of the analysis will be presented in the CSR.

Details of the analytical method used will be described in a bioanalytical report.

Anti-benralizumab antibodies

Serum will be collected pre-dose at Visit 3, as well as at Visits 6 and 8, to measure presence of ADA. Samples will be collected according to the study plan (see Table 2).

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

Neutralizing antibodies

Neutralizing antibodies (nAb) testing will occur on all samples that are ADA positive. Samples that are ADA-negative will not be tested for nAb. The presence or absence of neutralizing ADA will be determined using a validated bioanalytical method.

4.3.8 Handling of biological samples

4.3.8.1 Labeling and shipment of biological samples

The Principal Investigator is to ensure that samples are labeled 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),

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

4.3.8.2 Chain of custody of biological samples

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

The Principal Investigator at each study center is to keep full traceability of collected biological samples from the patients while in storage at the study center until shipment or disposal (where appropriate) and is to keep documentation of receipt of arrival.

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

AstraZeneca will maintain oversight of the entire life cycle through internal procedures, monitoring of study centers and auditing of external laboratory providers.

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

5. MANAGEMENT OF INVESTIGATIONAL PRODUCTS

5.1 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 (Table 4).

Table 4 Identity of investigational product

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

5.2 Labeling

Labeling of the IP will be carried out by AstraZeneca or designee in accordance with current Good Manufacturing Practice (GMP) and regulatory requirements of each country participating in the study. The labels will be translated into local languages where applicable.

5.3 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:

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

The center staff should not use affected IP and should immediately contact an AstraZeneca representative for further guidance. Damaged IP should be documented via IWRS/IVRS (refer to IWRS/IVRS manual for further details).

5.4 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 patient.

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.

5.5 Methods for assigning treatment groups

Randomization codes will be assigned strictly sequentially in each stratum as patients become eligible for randomization.

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

5.6 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).

Maintaining the blind to the patient's blood eosinophil counts

While not entirely specific, patients on active benralizumab treatment are expected to have lower blood eosinophil counts than patients on placebo. Procedures to mitigate unblinding on this basis include:

- From Week 0 on, monocyte counts will be redacted from central laboratory reports to prevent the Principal Investigator/designee from possibly deducing the 'eosinophil + basophil' contribution to the complete blood count.

- If the Investigator orders any local safety laboratory assessments, the requested tests should be restricted to the question at hand. For example, if a hemoglobin is desired, the Investigator should avoid ordering a complete blood cell count with differential.

- **Handling of labs obtained during the treatment period but ordered outside of the clinical trial**. Center staff who are directly involved in the patient's management should remain blinded to any eosinophil, basophil, and monocyte results included as part of outside lab reports. To help ensure this, each investigational center will designate an individual (eg, administrator or another ancillary person) not directly involved in patient management, to receive and blind any eosinophil, basophil, and monocyte results prior to the report being handed over to the center staff involved in the patient's management and prior to filing as a source document. Similarly, eosinophil and basophil results must be redacted from all communications with the Sponsor.

- In cases where the Investigator requires an eosinophil, basophil, or monocyte count for managing safety issues he/she may order these tests. AstraZeneca should be notified of all such cases.

5.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigator(s) or pharmacists at the study center from the IWRS/IVRS. Further detail on how to unblind a patient's treatment allocation will be described in the IWRS/IVRS user manual provided to each study center

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

AstraZeneca retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an IP 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 patient have been made and documented.

5.8 Investigational product administration and treatment 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 2.

Before IP administration

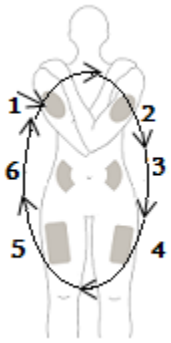
Prior to each IP administration:

- 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 4.2.4.1)

IP 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 2). The injection site must be recorded in the source documents and the eCRF at each treatment visit.

Figure 2 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. IP administration must be carried out in line with the Instruction.

After IP 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 IP 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

5.9 Management of IP-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).

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.

6. SAFETY REPORTING

6.1 Adverse events

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

6.1.1 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, ECG). 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.

6.1.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, screening/run-in, treatment, washout, follow-up), that fulfills 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 patient or may require medical intervention to prevent z of the outcomes listed above.

6.1.3 Recording of adverse events

6.1.3.1 Time period for collection of adverse events

All AEs, including SAEs, will be collected from the time the patient signs the informed consent throughout the treatment period and including the follow-up period (through Week 20).

6.1.3.2 Follow-up of unresolved adverse events

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

The requirement to follow-up AEs is not intended to delay database lock or production of the Clinical Study Report (CSR). These activities should proceed as planned with ongoing AEs if necessary.

Any follow-up information of ongoing SAEs after database lock will be reported to AstraZeneca.

6.1.3.3 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 IP (yes or no)
- Action taken with regard to IP
- AE caused patient's withdrawal from study (yes or no)
- Outcome.

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 6.1.2. 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. 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.

6.1.3.4 Causality collection

The Investigator will assess causal relationship between IP and each AE, 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'.

6.1.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient 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.

6.1.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared with baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

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 will use the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin 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.

6.1.3.7 Symptoms of the disease under study

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 6.1.2
- 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.

After randomization, asthma exacerbations should be recorded in the exacerbation eCRF (EXACA; see section 4.1.3). If the exacerbation fulfills any of the above criteria, the sign or symptom should also be recorded as an AE.

6.1.4 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.

6.1.5 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, 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 center personnel will inform appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** from when he or she becomes aware of it.

The designated AstraZeneca representative will work 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 AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other center personnel will 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** from when he or she becomes aware of it.

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

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

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

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

6.2 Overdose

- An overdose with associated AEs will be 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 will be reported on the Overdose CRF module only

If an overdose on an AstraZeneca study drug occurs in the course of the study, then Investigators or other center personnel will inform appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** from when he or she becomes aware of it.

The designated AstraZeneca representative will work 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, standard reporting timelines apply, see Section 6.1.5. For other overdoses, reporting should be done within 30 days.

6.3 Pregnancy

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

6.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP 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 patient was discontinued from the study.

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

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs (see Section 6.1.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy (PREGREP) module in the CRF will be used to report the pregnancy and the pregnancy outcome (PREGOUT) module will be used to report the outcome of the pregnancy.

6.3.2 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.

7. EVALUATION AND CALCULATION OF VARIABLES

7.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock
- Analyses will be performed by AstraZeneca or its representatives
- The SAP will be prepared prior to first patient randomized and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data

7.2 Sample size estimate

Patients will be stratified by blood eosinophil count <300 or ≥300 cells/μL and by region and then approximately 200 patients will be randomized to SC benralizumab 30 mg or placebo in a 1:1 ratio. The stratification will be done to remove potential confounding effects of geographic region and eosinophil levels on the treatment effect. The study is powered for the primary efficacy endpoint analysis of change from baseline in pre-BD FEV_1 at Week 12. Assuming a standard deviation of 350 mL and a two-sided 5% level t-test, the study has 80% power to detect a true treatment difference (benralizumab – placebo) of 140 mL and 90% power to detect a true treatment difference of 162 mL. Based on the assumptions above, the minimum difference that would be statistically significant at the 5% level is 98 mL.

7.3 Definitions of analysis sets

All efficacy analyses will be performed using an Intent-to-Treat (ITT) approach 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 population.

7.3.1 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.

7.3.2 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 to participate in the study will be included up to the date of their study termination.

7.3.3 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 one or several occasions received active treatment will be classified as active. If a patient has received both active dose regimens, then the patient will be classified as the higher active dose regimen. All safety summaries will be based on this analysis set.

7.3.4 Pharmacokinetic analysis set

All patients who received benralizumab and from whom PK blood samples were obtained are assumed not to be affected by factors such as protocol violations. Those patients 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.

7.3.5 Anti-drug Antibody analysis set

All patients in the safety analysis set who received at least 1 dose of IP will be included in the ADA analysis set. Patients will be classified the same way as in the safety analysis set. ADA summaries will be based on this analysis set.

7.4 Variables for analyses

7.4.1 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 Week 0 and the conclusion of EOT visit, inclusive.

7.4.1.1 Forced expiratory volume in 1 second

Change from baseline in pre-BD FEV_1 is the primary efficacy endpoint of this study. It will be calculated for Weeks 4, 8, and 12, as the post-baseline value minus the baseline value (pre-BD FEV_1 at Week 0). If the Week 0 pre-BD measurement is missing, the last non-missing pre-BD value before Week 0 will be used as baseline instead.

7.4.1.2 Asthma exacerbations

The number of exacerbations experienced by a patient throughout the study period will be calculated using the following rule:

The start of an exacerbation is defined as the start date of systemic corticosteroids or the start date of a temporary increase in a stable oral corticosteroid background dose, or the start date of

hospital admission, whichever occurs earlier. The end date is defined as the last day of systemic corticosteroids or the last day of a temporary increase in a stable oral corticosteroid background dose, or the date of discharge from a hospital, whichever occurs later.

Additional systemic corticosteroid treatments, emergency room /urgent care visits requiring use of systemic corticosteroids, or inpatient hospitalization due to asthma occurring during an exacerbation should not be regarded as a new exacerbation. In order to be counted for as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled.

Maximum follow-up time for a patient is approximately 20 weeks; defined as the time from randomization to the date of Visit 8. For a patient lost to follow-up, this will be defined as the time from randomization to the time point after which an exacerbation could not be assessed.

For each patient, the number of exacerbations and total follow-up time will be calculated.

7.4.2 Calculation or derivation of safety variable(s)

7.4.2.1 Safety variables

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

Change from baseline (Week 0) to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. Adverse events will be summarized by means of descriptive statistics and qualitative summaries.

7.4.2.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuations due to AEs.

Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

7.4.3 Calculation or derivation of patient reported outcome variables

7.4.3.1 Asthma symptom score

Asthma symptoms during nighttime and daytime will be recorded by the patient each morning and evening in the Asthma Daily Diary. Symptoms will be recorded using a scale of 0-3, where 0 indicates no asthma symptoms. Asthma symptom daytime score (recorded in the evening), nighttime score (recorded in the morning), and total score will be calculated and presented separately. The daily asthma symptom total score will be calculated by taking the sum of the nighttime and daytime asthma symptom scores recorded each day. If a patient is missing a value for either nighttime or daytime asthma symptom score on a given day, then the total score for that day will be set to missing.

The secondary outcome variable is the weekly mean daily asthma symptom total score. Weekly means for daytime and nighttime scores will also be calculated.

7.4.3.2 Asthma Control Questionnaire (ACQ-6)

The outcome variable for ACQ-6 will be the change in mean score from baseline (Week 0) to EOT (Week 12).

Asthma control responder status will be evaluated as a supportive analysis. Patients will be categorized according to the following limits (Juniper et al 2005):

- ACQ-6 (EOT – baseline) $\leq$-0.5 $\rightarrow$ Improvement
- -0.5< ACQ-6 (EOT – baseline) <0.5 $\rightarrow$ No change
- ACQ-6 (EOT – baseline) $\geq$0.5 $\rightarrow$ 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 EOT in ACQ 6 $\leq$ 0.5 and 0 otherwise.

Additionally, patients will be categorized according to their ACQ-6 defined asthma control stratus at the end of treatment using the following score thresholds (Juniper et al 2006):

- ACQ-6 (EOT) $\leq$0.75 $\rightarrow$ Well controlled
- 0.75< ACQ-6 (EOT) <1.5 $\rightarrow$ Partly controlled
- ACQ-6 (EOT) $\geq$1.5 $\rightarrow$ Not well controlled

7.4.3.3 Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12)

The AQLQ(S)+12 score will be summarized by domain (4 domains) and for overall. The outcome variable for the AQLQ(S)+12 will be the change in mean score from baseline (Week 0) to EOT (Week 12).

Patients will also be categorized according to the following limits:

- AQLQ(S)+12 (EOT – baseline) $\geq$0.5 $\rightarrow$ Improvement
- -0.5 < AQLQ(S)+12 (EOT – baseline) <0.5 $\rightarrow$ No change
- AQLQ(S)+12 (EOT – baseline) $\leq$-0.5 $\rightarrow$ Deterioration.

An AQLQ(S)+12 responder will be defined as a patient who had improvement on AQLQ(S)+12, ie, an AQLQ(S)+12 responder variable takes value 1 if change from baseline to EOT in AQLQ(S)+12 $\geq$0.5 and 0 otherwise.

7.4.3.4 Electronic diary variables

Rescue medication use

The number of rescue medication inhalations and nebulizer treatments taken will be recorded by the patient in the Asthma Daily Diary twice daily. Daytime use is recorded in the evening and

nighttime use is recorded in the morning. Inhaler usage will be reported as the number of puffs in a given period, whereas nebulizer use will be reported as the number of times. The number of inhalations of rescue medication and nebulizer treatments captured in the eDiary each day will be calculated per patient. If a patient is missing a value for either morning or evening rescue medication on a given day, then the total rescue medication use for that day will be set to missing. The number of inhalations (puffs) per day will be calculated as follows:

Number of night inhaler puffs + 2 x [number of night nebulizer times] + number of day inhaler puffs + 2 x [number of day nebulizer times].

Weekly mean number of inhalations (puffs) per day will be calculated as the outcome variable.

Nights with awakening due to asthma

Weekly mean number (percentage) of nights with awakening due to asthma that required rescue medication will be calculated as the outcome variable.

Home peak expiratory flow (morning and evening)

Weekly mean changes from baseline in morning and evening PEF will be calculated.

7.4.4 Calculation or derivation of pharmacokinetic variables

Due to the limited sampling schedule, the PK assessment will be primarily based on the observed steady-state serum trough (pre-dose) concentrations, C_{trough}. Empirical evaluation of potential impact of demographic covariates and ADA on C_{trough} will be conducted. The PK data and parameters from this study will be reported in the CSR.

7.4.5 Calculation or derivation of immunogenicity variables

ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer). The presence of nAb will be tested in all ADA-positive samples time points using a ligand binding assay.

7.5 Methods for statistical analyses

The analysis of the primary and secondary endpoints will include all data captured during the 12-week 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.

Demography and baseline characteristics will be summarized by treatment group for the full analysis set. In the event that there are major differences between the full analysis set and safety analysis set, these summaries will also be repeated for the safety analysis set.

7.5.1 Primary analysis method(s)

Change from baseline in pre-BD FEV_1 at Week 12 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-specified visits (up to the EOT Visit). Treatment group will be fitted as the explanatory variable, and eosinophil level (<300 or ≥300 cells/μL), region, and baseline pre-BD FEV_1will be fitted as covariates. Visit will be fitted as a categorical variable, and 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+eosinophil level (<300 or ≥300 cells/μL) + region + visit+ treatment*visit*

7.5.2 Secondary analysis methods

7.5.2.1 Analysis methods for secondary efficacy variables

Secondary efficacy endpoints include:

- Change from baseline in total asthma symptom score at Week 12
- Change from baseline in total asthma rescue medication use (average puffs/day) at Week 12
- Change from baseline in morning and evening PEF at Week 12
- Change from baseline in nighttime awakenings due to asthma and requiring rescue medication at Week 12
- Asthma exacerbations
- Change from baseline in ACQ-6 score at Week 12
- Change from baseline in AQLQ(S)+12 total and domain scores at Week 12

Change from baseline in total asthma symptom score, total rescue medication use, morning and evening PEF (separately), nighttime awakening due to asthma and requiring rescue medication, and mean ACQ-6 score at Week 12 will all be analyzed in the same way as described in Section 7.5.1 for pre-BD FEV_1. The number of asthma exacerbations and total follow-up time will be presented for each treatment group.

Change in mean score from baseline for AQLQ(S)+12 (including the domain scores) will be analyzed by fitting an ANCOVA model with treatment, eosinophil level (< or ≥300 cells/μL), region, and baseline value as covariates.

Responder variables for ACQ-6 (yes/no) and AQLQ(S)+12 (yes/no) will be analyzed using a logistic regression model with covariates of treatment, eosinophil level (<300 or ≥300 cells/μL), region, and baseline value.

7.5.2.2 Analysis methods for safety variables

AEs will be summarized by means of counts by study period (treatment period and follow-up period). AEs will be listed for each patient and summarized by System Organ Class (SOC) and

Preferred Term (PT) assigned to the event by MedDRA. Laboratory safety variables will be summarized using standard summary statistics and plots as appropriate. Other safety variables will be summarized as appropriate. Further details will be provided in the SAP.

Laboratory data for hematology and clinical chemistry will be summarized. The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will also be given. Shifts from normal to abnormal between baseline and each post-baseline time point will be evaluated for urinalysis. Changes in vital signs will be examined at each visit and endpoint. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will be presented. Shifts from normal to abnormal between baseline and follow-up will be evaluated for the physical examination.

7.5.2.3 Analysis methods for pharmacokinetic variables

The PK analyses will be performed at or under the guidance of AstraZeneca Research and Development.

Benralizumab serum concentrations will be summarized using descriptive statistics at each visit by treatment group. Serum concentration-time profiles of benralizumab by treatment group will be generated. The potential influence of demographic covariates such as body weight, race, gender and age will be evaluated. Impact of ADA on PK will also be assessed. Serum concentrations of benralizumab, summary statistics, empirical covariate analysis results and PK profiles will be provided in the CSR or as an addendum to the CSR.

7.5.2.4 Analysis method for blood eosinophil levels

Blood eosinophil levels will be summarized using standard summary statistics and plots at each visit by treatment group.

7.5.2.5 Analysis method for immunogenicity variables

Anti-drug antibodies (ADA) to benralizumab will be summarized using descriptive statistics at each visit by treatment group. ADA titers-time profiles of benralizumab by treatment group will be generated. The impact of ADA on PK and eosinophil level will be assessed. The potential association of ADA with safety and efficacy will be evaluated. The association of ADA titer with nAb phenotype (positive or negative), benralizumab concentration, blood eosinophil levels, and efficacy will be evaluated for ADA positive patients only.

7.5.3 Subgroup analysis

To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analyses and statistical modeling including testing for interaction between treatment and covariates will be performed for the following factors: eosinophil level ($<$ and $\geq$ 300 cells/μL), gender, age ($<$65 and $\geq$65 years), BMI ($\leq$35, $>$35 kg/m2), and race. Data will be analyzed using a repeated measures model similar to the primary analysis and the same output will be presented for each subgroup as for the primary analysis. For the statistical modeling

including interaction effects, the estimate of the interaction effects will be presented together with the corresponding p-value.

These analyses are to be considered exploratory and will be performed on the full analysis set.

7.5.4 Sensitivity analysis

Sensitivity analyses for the primary endpoint based on different missing data mechanism assumptions including those expected to be more conservative such as missing not at random will be used to explore the robustness of any treatment effect, including multiple imputation approaches. Full details of the sensitivity analyses will be pre-specified in SAP and documented prior to database lock of the studies

7.5.5 Interim analysis

There is neither an unblinded data review nor interim analysis planned for this study.

8. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

8.1 Training of study center personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol (CSP) 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 will maintain a record of all individuals involved in the study (medical, nursing and other staff).

8.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study center, 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 patient's medical records at the hospital or practice, and other records relevant to the study)

including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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.

8.2.1 Source data

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

8.2.2 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.

8.2.3 Study agreements

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

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

8.2.4 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

8.3 Study timetable and end of study

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

The study is expected to start in Q1 2015 and to end by Q1 2016.

The study may be terminated at individual study centers if the study procedures are not being performed according to 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.

8.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Center staff according to the Data Management Plan.

AEs 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. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Center.

The 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 eCRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigator will ensure 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. ETHICAL AND REGULATORY REQUIREMENTS

9.1 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/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

9.2 Patient data protection

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

9.3 Ethics and regulatory review

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

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

The EC should approve all advertising used to recruit patients 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 enrollment of any patient 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 Regulatory Authorities, ECs and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the ECs/Institutional Review Board (IRB) 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 Principal Investigator so that he/she can meet these reporting requirements.

9.4 Informed consent

The Principal Investigator(s) at each study center will:

- Ensure each patient or legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study (before any study procedures are performed) as per local requirements. The ICF needs to be adjusted as per local requirements.
- Ensure each patient or legal guardian is notified that they are free to discontinue from the study at any time.
- Ensure that each patient or legal guardian is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient or legal guardian provides signed and dated Informed Consent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent(s) is/are stored in the Investigator's Study File and kept for a period that is complaint with GCP/local regulatory requirements, whichever is longer.
- Ensure a copy of the signed Informed Consent Form is given to the patient.

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the Informed Consent Form that is approved by an Ethics Committee.

9.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International coordinating Investigator and 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 regulatory authority 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 Principal Investigator(s). For distribution to EC see Section 9.3.

If a protocol amendment requires a change to a study center's ICF, AstraZeneca and the study 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.

9.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the study center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation , and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency or other body about an inspection or an audit at the study center.

10. LIST OF REFERENCES

Bateman et al 2010
Bateman ED, Reddel HK, Eriksson G, Peterson S, Ostlund O, Sears MR, et al. Overall asthma control: The relationship between current control and future risk. American Academy of Allergy, Asthma & Immunology. 2010;125(3):600-08.

Bousquet et al 1990
Bousquet J, Chanez P, Lacoste JY, Barnéon G, Ghavanian N, Enander I, et al. Eosinophilic inflammation in asthma. N Engl J Med. 1990 Oct 11;323(15):1033-9.

Busse et al 2010
BusseWW, Katial R, Gossage D, Sari S, Wang B, Kolbeck B, et al. Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti–IL-5 receptor a antibody, in a phase I study of subjects with mild asthma. J Allergy Clin Immunol. 2010 Jun;125(6):1237-44.

Castro et al 2011
Castro M, Mathur S, Hargreave F, Boulet L-P, Xie F, Young J, et al. poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2011;184:1125-32.

Castro et al 2014
Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, for uncontrolled eosinophilic asthma. Lancet Respir Med. 2014 Oct 09 (online).

Di Franco et al 2003
Di Franco A, Bartoli ML, Carnevali S, Cianchetti S, Bacci E, Dente FL, et al. Analysis of sputum cell counts during spontaneous moderate exacerbations of asthma in comparison to the stable phase. J Asthma. 2003 Apr;40(2):155-62.

GINA 2011
Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) December 2011. Available from: URL: http://www.ginasthma.org/guidelines-ginareport-global-strategy-for-asthma.html.

Gossage et al 2012
Gossage DL, Laviolette M, Gauvreau GM, Leigh R, Kolbeck R, Wu1 Yet al. Depletion Of Airway Eosinophils By Benralizumab An Anti-Il5 Receptor Alpha Monoclonal Antibody. Am J Respir Crit Care Med. 185;2012:A3961.

Juniper et al 2005
Juniper EF, Svensson K, Mörk AK, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med. 2005;99:553-58.

Juniper et al 2006
Juniper EF, Bousquet J, Abetz L, Bateman ED,The GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med. 2006;100:616-21.

Kolbeck et al 2012
Kolbeck R, Kozhich A, Koike M, Peng L, Andersson CK, Damschroder MM, et al. MEDI-563, a humanized anti–IL-5 receptor a mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. J Allergy Clin Immuno. 2010, Jun;125(6):1344-53.

Lieberman et al 2010
Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 2010 Sep;126(3):477-80.e1-42.

Louis et al 2000
Louis R, Lau LC, Bron AO, Roldaan AC, Radermerker M, Djukanovic R. The relationship between airways inflammation and asthma severity. Am J Respir Crit Care Med. 2000 Jan;161(1):9-16.

Masoli et al 2004
Masoli M, Holt S, Weatherall M, Beasley R. The dose-response relationship of inhaled corticosteroids in asthma. Curr Allergy Asthma Rep. 2004 Mar;4(2):144-8.

Miller et al 2005
Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function Testing. Eur Respir J 2005;26(1):153-61.

Molfino et al 2011
Molfino NA, Gossage D, Kolbeck R, Parker JM, Geba GP. Molecular and clinical rationale for therapeutic targeting of interleukin-5 and its receptor. Clin Exp Allergy. 2011;42;712-37.

Molfino et al 2012
Molfino NA, Nowak R, Silverman RA, Rowe BH, Smithline H, Khan F,et al Reductionin the number and severity of exacerbations following acute severe asthma: results of a placebo-controlled, randomized clinical trial with benralizumab. Am J Respir Crit Care Med;2012: 185:A2753.

NAEPP 2007
NAEPP 2007, *National Asthma Education Prevention Program. Expert Panel Report 3:Guidelines for the Diagnosis and Management of Asthma*. Available: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.

Ortega et al 2014
Ortega HG, Liu MC, Pavord ID, Brusselle GG, Fitzgerald JM, Chetta A, et al. Mepolizumab treatement in patients with severe eosinophilic asthma. N Engl J Med. 2014 Sep 25;371(13):1198-207.

Quanjer et al 2012
Quanjer PH, Stanojevic S, Cole TJ, Baur X, L Hall GL, Culver B, et al. Multi ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. 2012 Dec;40(6):1324-43.

Simpson et al 2006
Simpson JL, Scott R, Boyle MJ, Gibson PG. Inflammatory subtypes in asthma: assessment and identification using induced sputum. Respirology 2006;11(1):54-61.

Scott and Wardlaw 2006
Scott KA, Wardlaw AJ. Eosinophilic airway disorders. Semin Respir Crit Care Med. 2006; 27(2):128-33.

Sorkness et al 2008
Sorkness RL, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Chung KF, et al. Lung function in adults with stable but severe asthma: air trapping and incomplete reversal of obstruction with bronchodilation. J Appl Physiol, 2008;104:394–403,.

Takatsu et al 1994
Takatsu K, Takaki S, Hitoshi Y. Interleukin-5 and its receptor system: implications in the immune system and inflammation. Adv Immunol. 1994;57:145-90.

Toba et al 1999
Toba K, Koike T, Shibata A, Hashimoto S, Takahashi M, Masuko M, et al. Novel technique for the direct flow cytofluorimetric analysis of human basophiles in unseparated blood and bone marrow, and the characterization of phenotype and peroxidase of human basophiles. Cytometry. 1999 Mar 1;35(3):249-59.

Wenzel 2012
Wenzel S E. Asthma phenotypes: the evolution from clinical to molecular approaches. 2012 May 4;18(5):716-25.

Zhang and Wenzel 2007
Zhang JY, Wenzel SE. Tissue and BAL based biomarkers in asthma. Immunol Clin North Am. 2007 Nov;27:623-32.