Appendix 12.1.1
Protocol and Protocol Amendments

VERSION OF PROTOCOL OR PROTOCOL AMENDMENT

Document	Date of issue
First final version of the protocol prior to any amendments	14 December 2015

AstraZeneca

Clinical Study Protocol	
Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00033
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A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study to Evaluate the Potential Effect of Benralizumab on the Humoral Immune Response to the Seasonal Influenza Vaccination in Adolescent and Young Adult Patients with Severe Asthma (ALIZE)

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 3b Study to Evaluate the Potential Effect of Benralizumab on the Humoral Immune Response to the Seasonal Influenza Vaccination in Adolescent and Young Adult Patients with Severe Asthma (ALIZE)

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Study center(s) and number of patients planned

This study will be conducted in the United States in approximately 35 study centers. Target is to randomize approximately 100 patients.

Study period		Phase of development
Estimated date of first patient enrolled	Q3 2016	Phase 3b
Estimated date of last patient completed	Q1 2017	

Objectives

(a) Primary Objective

Objective	Endpoint(s)
To evaluate the potential effect of benralizumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult patients with severe asthma	• Post-dose strain-specific hemagglutination-inhibition (HAI) antibody geometric mean fold rises (GMFRs) from Week 8 • Post-dose strain-specific serum HAI antibody geometric meant titers (GMTs) obtained at Week 12 • Proportion of patients who experience a strain-specific post-dose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in HAI antibody titer from Week 8 • Proportion of patients who achieve a strain-specific post-dose HAI antibody titer ≥40 at Week 12

(b) Secondary Objectives

Objective	Endpoint(s)
To further evaluate the potential effect of benralizumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult patients with severe asthma	• Proportion of patients who achieve a strain-specific post-dose HAI antibody titer ≥320 at Week 12 • Post-dose strain-specific microneutralization (MN) antibody GMFRs from Week 8 • Post-dose strain-specific serum MN GMTs obtained at Week 12 • Proportion of patients who experience a strain-specific post-dose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in MN antibody titer from Week 8
To assess the potential effect of benralizumab on asthma control	• Change from baseline in mean Asthma Control Questionnaire-6 (ACQ-6) score at Week 12

(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 investigate the potential effect of a fixed dose of benralizumab (30 mg) administered subcutaneously (SC) on antibody responses following seasonal influenza virus vaccination.

Approximately 100 patients 12-21 years of age with severe asthma will be randomized to receive SC benralizumab 30 mg or placebo administered at Weeks 0, 4, and 8.

After enrolment and confirmation of entry criteria, patients will proceed to a screening period of a minimum of 2 weeks to allow adequate time for all of the eligibility criteria to be evaluated before being randomized at Visit 3. Patients who continue to meet eligibility criteria will be randomized on Week 0 to receive 3 SC doses (at Weeks 0, 4, and 8) of benralizumab 30 mg or placebo. Patients will receive 1 dose of seasonal influenza vaccine intramuscularly (IM) at Week 8. Serum samples for evaluation of antibody response will be drawn at Week 8 and Week12. An End of Treatment (EOT) will also be conducted at Week 12 and a Follow-up visit will be conducted at Week 20.

Patients will be maintained on their currently prescribed ICS-LABA therapy(ies) without change from enrolment throughout the screening and treatment period.

Target patient population

Male and female adolescent patients 12 to 21 years of age, inclusive, with severe asthma will be enrolled. Fifty percent or more of the patients will be 12 to 17 years of age.

Investigational product, dosage and mode of administration

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

Comparator, dosage and mode of administration

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

Duration of treatment

Following enrolment, patients will enter a 2 to 3 week screening period followed by a 12-week double-blind, randomized treatment period, with the last dose of benralizumab/placebo

administered at Week 8. An End of Treatment (EOT) will be conducted at Week 12 and a Follow-up visit will be conducted at Week 20.

The total planned study duration is a maximum of 23 weeks.

Statistical methods

The benralizumab versus placebo antibody response following seasonal influenza virus vaccination will be assessed by

- Post-dose strain-specific HAI antibody geometric mean folder rises (GMFRs) from Week 8
- Post-dose strain-specific HAI antibody geometric mean titers (GMTs) obtained at Week 12
- Proportion of patients who experience a strain-specific post-dose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in HAI antibody titer from Week 8
- Proportion of patients who achieve a strain-specific post-dose HAI antibody titer ≥40 at Week 12
- Proportion of patients who achieve a strain-specific post-dose HAI antibody titer ≥320 at Week 12
- Post-dose strain-specific microneutralization (MN) antibody GMFRs from Week 8
- Post-dose strain-specific serum MN antibody GMTs obtained at Week 12
- Proportion of patients who experience a strain-specific post-dose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in MN antibody titer from Week 8

The analysis of the anti-influenza antibody response endpoints–strain-specific GMFRs and GMTs–will be performed on the immunogenicity analysis set, defined as all randomized patients who received at least 1 dose of planned investigational product (ie, 1 dose of influenza vaccine plus 1 dose of benralizumab or placebo), had pre- and post-dose HAI antibody measurements, had pre- and post-dose MN antibody measurements, and had no protocol deviation judged to have the potential to interfere with the generation or interpretation of an humoral response to the influenza vaccine. GMFRs and GMTs will be summarized by treatment group, and the group ratio of GMFRs (influenza vaccine divided by benralizumab and influenza vaccine) and GMTs and their corresponding 90% confidence intervals (CIs) will be constructed.

The antibody response to the influenza vaccine is defined as a ≥4-fold rise in HAI from Week 8. The proportion of patients who experience a post-dose HAI antibody response at Week 12 and corresponding 90% Clopper-Pearson exact CI will be summarized by treatment group.

The proportion of patients who achieve a post-dose HAI antibody titer ≥40 at Week 12 and corresponding 90% Clopper-Pearson exact CI will be summarized by treatment group.

The proportion of patients who achieve a post-dose HAI antibody titer ≥320 at Week 12 and corresponding 90% Clopper-Pearson exact CI will be summarized by treatment group.

The antibody response to the influenza vaccine is also defined as a ≥4-fold rise in MN antibody from Week 8. The proportion of patients who experience a post-dose MN antibody response at Week 12 and corresponding 90% Clopper-Pearson exact CI will be summarized by treatment group.

For GMFR and GMT, the geometric least square mean ratio between treatment groups (placebo/benralizumab) will be calculated via an analysis of covariance (ANCOVA) model on the log-transformed variable, adjusting for treatment group. The least square geometric mean ratio will be provided with associated 90% CI.

No interim blinded review is planned.

No formal statistical hypotheses will be tested. The sample size justification is based on the precision of the estimate of the GMTs (as $GMT_{vaccine}$ / $GMT_{benralizumab+vaccine}$). With 50 patients per arm, the 90% CI for the GMT ratio would be 0.67 to 1.48, assuming an observed ratio of 1, and that the log (post-dose HAI antibody titer or post-dose MN antibody titer) is normally distributed with a standard deviation (SD) of 1.2 on the natural log scale (Langley et al 2013).

All safety parameters will be analyzed descriptively. Safety analyses will be based on the safety analysis set, defined as all patients who received at least 1 dose of 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
ARE	Antibody Response Evaluation
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
Beta-hCG	Beta- human chorionic gonadotropin
BMI	Body mass index
CI	Confidence interval
CO_2	Carbon dioxide
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
EU	European Union
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
Gamma-GT	Gamma-glutamyl transpeptidase
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMFR	Geometric mean fold rises
GMP	Good Manufacturing Practice

Abbreviation or special term	Explanation
GMT	Geometric mean titers
HAI	Hemagglutination-inhibition
HCG	Human chorionic gonadotropin
HCP	Health care provider
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICI	International Coordinating Investigator
ICS	Inhaled corticosteroids
IL	Interleukin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-5Rα	Interleukin-5 receptor alpha subunit
IM	Intramuscular
IP	Investigational product
IPD	Premature IP Discontinuation
IRB	Institutional Review Board
ITT	Intent-to-Treat
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
MN	Microneutralization antibodies to influenza vaccine
PK	Pharmacokinetic(s)
Post-BD	Post-bronchodilator
Pre-BD	Pre-bronchodilator
PRO	Patient reported outcome
RBC	Red blood cell
SABA	Short-acting β_2 agonists
SAE	Serious adverse event

Abbreviation or special term	Explanation
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 has become more common in both children and adults around the world in recent decades. It 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 (GINA 201, 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 2015, 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 2015, 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, Laviolette et al 2013). Also, a recent dose-finding trial in severe asthma proved benralizumab to have benefit across a range of asthma outcomes including reductions in asthma exacerbations, improvements in lung function, and reduction in symptoms (Castro et al 2014).

Benralizumab is currently being studied in Phase 3 in severe asthmatics with a history of exacerbations, still symptomatic despite using medium-to-high dose ICS/LABAs with or without oral corticosteroids or additional controller medications.

As benralizumab depletes eosinophils, it is important to determine if benralizumab affects functioning of the immune system, especially in adolescents and young adults. In this study, a functional response of the immune system will be assessed by measuring antibody responses to the influenza vaccine.

1.2 Rationale for study design, doses and control groups

This study is designed to investigate the potential effect of benralizumab on the antibody response to the seasonal influenza virus vaccine in patients 12-21 years of age with asthma. Benralizumab (30 mg) will be given subcutaneously (SC) at Weeks 0, 4, and 8 weeks, at which time benralizumab levels will reach steady state. Patients will then receive 1 dose of intramuscular (IM) seasonal influenza virus vaccine at Week 8 and samples drawn at Week 8 and Week 12 to measure the antibody response to the influenza virus

The immune response, as assessed by evaluation of antibody responses to the influenza vaccine in the group receiving benralizumab versus placebo will be assessed by

- Post-dose strain-specific HAI antibody geometric mean folder rises (GMFRs) from Week 8
- Post-dose strain-specific HAI antibody geometric mean titers (GMTs) obtained at Week 12
- Proportion of patients who experience a strain-specific post-dose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in HAI antibody titer from Week 8
- Proportion of patients who achieve a strain-specific post-dose HAI antibody titer ≥40 at Week 12
- Proportion of patients who achieve a strain-specific post-dose HAI antibody titer ≥320 at Week 12
- Post-dose strain-specific MN antibody GMFRs from Week 8
- Post-dose strain-specific serum MN antibody GMTs obtained at Week 12
- Proportion of patients who experience a strain-specific post-dose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in MN antibody titer from Week 8

The benralizumab dose (30 mg SC, fixed) is based on all available safety and efficacy 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 not restricted per protocol 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 2015). 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). To date, there have been no identified risks. 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 is to assess the effect of benralizumab on the humoral immune response following seasonal influenza virus vaccination in patients 12-21 years of age with asthma. Mild problems following inactivated flu vaccine may include soreness, redness, or swelling where the shot was given, as well as sore, red or itchy eyes, hoarseness, cough, fever, aches, headache, itching, and fatigue (CDC 2014). Very rarely, as with all vaccines, anaphylaxis may occur. Benefits would include probable protection against developing influenza in the upcoming flu season.

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 investigate the potential effect of a fixed dose of benralizumab (30 mg) administered SC on the humoral immune response following seasonal influenza virus vaccination.

Approximately 100 patients 12-21 years of age with severe asthma will be randomized to receive SC benralizumab 30 mg or placebo administered at Weeks 0, 4, and 8. Fifty percent or more of the patients will be 12 to 17 years of age.

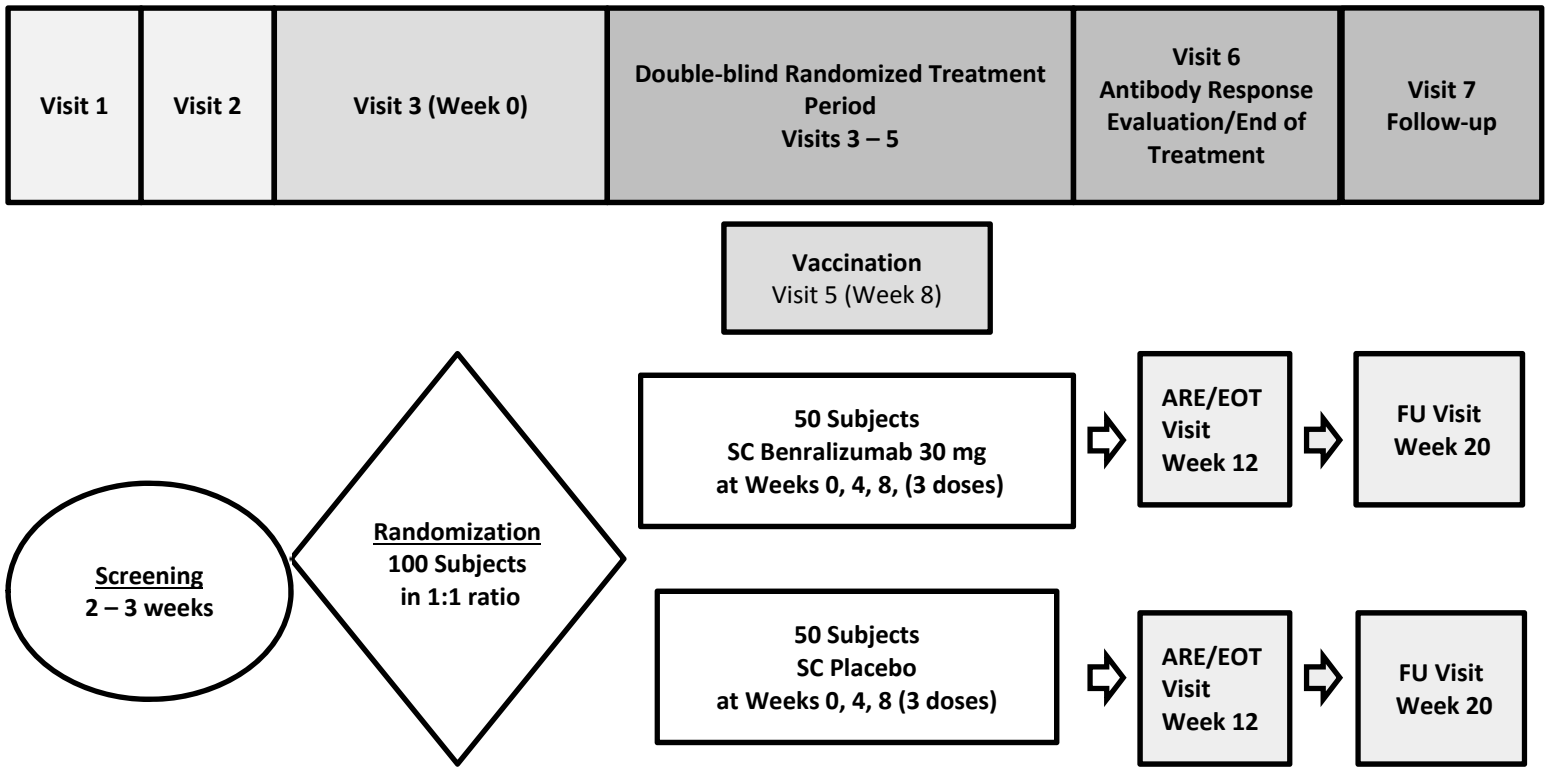
Patients will receive 1 dose of seasonal influenza virus vaccine IM at Week 8. Samples for evaluation of antibody response will be drawn at Week 8 and Week 12.

After enrolment and confirmation of entry criteria, patients will proceed to screening period of a minimum of 2 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Patients who continue to meet the eligibility criteria will be randomized at Week 0 to receive 3

SC doses (at Weeks 0, 4, and 8) of benralizumab 30 mg or placebo. Patients will receive 1 dose of seasonal influenza virus vaccine IM at Week 8. Samples for evaluation of antibody response will be drawn at Week 8 and Week 12. The End of Treatment (EOT) will be conducted at Week 12 and a Follow-up (FU) visit will be conducted at Week 20.

Patients will be maintained on their currently prescribed ICS-LABA therapy(ies) without change from enrollment throughout the screening and treatment period.

Figure 1 Study flow chart



2. STUDY OBJECTIVES

2.1 Primary Objective

Objective	Endpoint
To evaluate the potential effect of benralizumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult patients with severe asthma	• Post-dose strain-specific hemagglutination-inhibition (HAI) antibody geometric mean fold rises (GMFRs) from Week 8 • Post-dose strain-specific serum HAI antibody geometric meant titers (GMTs) obtained at Week 12 • Proportion of patients who experience a strain-specific post-dose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in HAI antibody titer from Week 8 • Proportion of patients who achieve a strain-specific post-dose HAI antibody titer ≥40 at Week 12

2.2 Secondary Objectives

Objective	Endpoint
To further evaluate the potential effect of benralizumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult patients with severe asthma	• Proportion of patients who achieve a strain-specific post-dose HAI antibody titer ≥320 at Week 12 • Post-dose strain-specific microneutralization (MN) antibody GMFRs from Week 8 • Post-dose strain-specific serum MN antibody GMTs obtained at Week 12 • Proportion of patients who experience a strain-specific post-dose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in MN antibody titer from Week 8
To assess the potential effect of benralizumab on asthma control	• Change from baseline in mean Asthma Control Questionnaire-6 (ACQ-6) score at Week 12

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, DISCONTINUATION, AND WITHDRAWAL CRITERIA

3.1 Inclusion criteria

For inclusion in the study patients must fulfill all of the following criteria:

1. Written informed consent/assent as appropriate with local guidance 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 patients aged 12 to 21 years, inclusive, at the time of Visit 1

3. Women of childbearing potential (WOCBP) must use an effective form of birth control (confirmed by the Investigator). Effective forms of birth control includes: true sexual abstinence, a vasectomized sexual partner, Implanon® , female sterilization by tubal occlusion, any effective IUD Intrauterine device/IUS Ievonorgestrel Intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch ™ or Nuvaring™. WOCBP must agree to use an 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.

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. Documented history of current treatment with ICS and LABA. The ICS and LABA can be parts of a combination product or given by separate inhalers. The ICS dose must be greater than or equal to 500 μg/day fluticasone propionate dry powder formulation or equivalent daily.

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

- Additional asthma controller medications (eg, LTRAs, short- and long-acting anti-muscarinics, theophylline, oral corticosteroids, etc) that have been used for at least 30 days prior to Visit 1 are allowed (see Section 3.5.2.1 for restricted therapies)

7. Morning pre-bronchodilator forced expiratory volume in 1 second (FEV_1) of >50% predicted at Visit 1 or Visit 2.

8. Evidence of asthma as documented by either:

   - Airway reversibility (FEV_1 $\geq$12% and 200 ml) demonstrated at Visit 1 or Visit 2 using the Maximum Post-bronchodilator Procedure OR

   - Airway reversibility documented in the previous 12 months prior to Visit 1

   Note: **All patients must have reversibility testing performed before randomization to establish a baseline characteristic even if historical documentation is used to meet this criterion.**

   If historical reversibility is being used to meet this criterion, the relevant historical pre- and post-bronchodilator results must be entered into the electronic case report form (eCRF).

   If patients do not demonstrate airway reversibility at either Visit 1 or Visit 2 and historical reversibility is not available for evidence of asthma, the patient must not enter the treatment period and must be rescreened, if appropriate. If re-screened, the site should reiterate the need to withhold short- and long-acting bronchodilators as required in Section 5.1.2 prior to spirometry visits in an effort to meet this inclusion criterion.

Randomization criteria

9. For WOCBP: have a negative urine pregnancy test prior to administration of the IP at Visit 3

10. Not well controlled asthma as documented by either

    - An ACQ-6 $\geq$1.5 OR

    - A peak flow of 60-80% predicted OR

    - An exacerbation, 1 or more, that required oral corticosteroids in the previous year OR

    - Any 1 of the following assessed by patient recall over the previous 2-4 weeks

- Asthma symptoms >2 days/week; OR
- Nighttime awakenings 1 or more/week; OR
- Short acting β_2-agonist use for symptom control (not for prevention of exercise-induced asthma) >2 days/week.

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, 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 IP formulation or influenza vaccine

4. Allergy to eggs

5. History of anaphylaxis to any biologic therapy

6. History of Guillain-Barré syndrome

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

8. Any clinically significant abnormal findings in physical examination, vital signs, baseline ECG, 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. 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

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

11. Current smokers

12. 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/assent 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/assent was obtained

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

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

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

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

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

18. Receipt of an influenza vaccine within 90 days prior to randomization

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

20. Previously received benralizumab (MEDI-563)

21. Change to allergen immunotherapy or initiation of new allergen immunotherapy is not allowed within 30 days prior to the date of informed consent/assent. Changes to

allergen immunotherapy are not allowed during the conduct of the study. 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 IP administration.

22. Planned surgical procedures during the conduct of the study

23. Currently breastfeeding or lactating women

24. Concurrent enrollment in another drug-related interventional clinical trial

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

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

27. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.5 times the upper limit of normal (ULN) confirmed during screening period

28. Life threatening asthma defined as episodes requiring intubation associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma related syncopal episodes

Exclusion criterion at randomization

29. Poorly controlled asthma during the screening period that requires treatment with oral corticosteroids or a hospitalization/emergency room visit for the treatment of asthma

30. Acute illness or evidence of significant active infection or known influenza infection during the current flu season

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

3.3 Patient enrolment 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/assent as appropriate with local guidance 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 patient 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 IP 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 Study Physician immediately, and a discussion should occur between the Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The 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/assent, 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 6 (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 4.1.1).

3.5.1.1 Background medication

Background asthma medications should be maintained at stable doses from Visit 1 until the end of the study. If changing the ICS/LABA dose or any other controller medication is judged as necessary by the Investigator or the patient's healthcare provider (HCP), the justification should be documented in the source and the change in the doses should be reflected in the eCRF.

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) **Changes to the patient's background controller regimen are discouraged during the study** unless judged medically necessary by the Investigator or the patient's HCP; 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 can be treated with oral or other systemic corticosteroids or other asthma therapies according to standard practice.

(b) **Asthma medication restrictions on the days of scheduled spirometry visits**

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 the patient's background medication are required prior to the spirometry as described below (also see Section 5.1.2).

Screening Visit 2: Patients will be asked to withhold their usual bronchodilator medications on the morning of scheduled spirometry measurements. Twice daily therapies containing bronchodilators should be withheld for 12- 24 hours; once daily therapies containing bronchodilators should be withheld for ≥24 hours for eligibility assessment. In addition, SABA should not be used within 6 hours of these spirometry assessments. If the patient has taken rescue SABA within 6 hours of the planned center visit spirometry, they can remain at the center until the 6-hour withholding time has been reached or return on another day within the visit window.

The patient's usual asthma medications may be administered following completion of the screening lung function procedures.

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 13 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 other drugs with a narrow therapeutic range, 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 1)

(e) Patients should not take any other excluded medications. A table with medication-related restrictions is presented in Appendix G.

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/assent, and for 16 weeks (5 half-lives) after last dose of IP (see Section 3.1, inclusion criteria 3 and 4; and Section 7.3.2)

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

3.6 Discontinuation from investigational product

Patients will be discontinued from IP 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 or Sponsor 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. Severe non-compliance with study protocol

6. Pregnancy

7. Lost to follow-up[1]

8. Development of any study specific criteria for discontinuation:

[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.

(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.

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 (IP and assessments) without prejudice to further treatment.

A patient/parent or legal guardian who withdraws consent/assent 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 enrollment/randomization code of the withdrawn patient cannot be reused.

3.8 Withdrawal of informed consent for donated biological samples

Samples taken for the evaluation of PK and ADA will be retained for repeat analysis of PK and ADA at AstraZeneca or designee for a maximum of 1 year following completion of the clinical study report (CSR). If a patient/parent or legal guardian withdraws consent/assent 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/assent immediately and that samples are disposed/destroyed.
- Ensures that the patient and AstraZeneca or designated CRO are informed about the sample disposal.

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

4. STUDY PLAN AND PROCEDURES

Table 1 Study Plan – Enrollment, screening period

Assessment/ activity	Refer to	Screening	
		V1	V2[a]
		(W -4 to W -2)	
Informed consent/assent	10.4	X	
Inclusion/exclusion criteria	3.1/3.2	X	X
Medical and asthma history [b]	4.1.1	X	
Complete physical examination	5.2.1.1	X	
Weight, Height, BMI	5.3.1	X	
Vital Signs	5.2.2	X	X
Local ECG	5.2.3	X	
Serum chemistry	5.2.4	X	
Hematology	5.2.4	X	
Urinalysis	5.2.4	X	
Serum concentration (theophylline)[c]	3.5.2.2	X	
Serology (hepatitis B,C; HIV-1; HIV-2)	5.3.4.1	X	
Serum pregnancy test	5.2.4.1	X	
Pre-bronchodilator FEV_1 [d]	5.1.2.1	X	X
Post-bronchodilator FEV_1[d]	5.1.2.1	X	X
Adverse events	7.1	X	X
Concomitant medication	3.5	X	X

[a] Visit 1 and Visit 2 can be combined if the patient has the time and they have not taken SABAs for 6 hours or their long-acting bronchodilator-containing therapy for 12-24 hours. If spirometry/reversibility procedures are actually planned at Visit 1 as a convenience, then the ICF/assent must be signed prior to Visit 1 and prior to instructing the patient to withhold any medication.

[b] To include influenza vaccination history.

[c] For patients on theophylline (see Section 3.5.2.2)

[d] Pre- and post-bronchodilator spirometry can be done at Visit 1 OR Visit 2. If patients do not demonstrate airway reversibility at either Visit 1 or Visit 2 and this is needed to qualify the patient for randomisation, the site should screen fail the patient.

BMI Body mass index; D Days; ECG Electrocardiogram; HIV Human immunodeficiency virus; V Visit; W Week.

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

Assessment/ activity	Refer to	Treatment			ARE/EOT	IPD	FU	Unsch
		V3	V4	V5	V6		V7	
		W0	W4	W8	W12		W20	
			Visit window (days) [a]					
		±0	±3	±3	±3	±3	±3	
Inclusion/exclusion criteria	3.1/3.2	X						
Randomization	3.3	X						
Administration of investigational product[c]	6.8	X	X	X				
Administration of influenza vaccine[e]				X				
Complete physical examination	5.2.1.1	X			X	X	X	
Brief physical examination	5.2.1.2		X	X				X
Vital Signs	5.2.2	X	X	X	X	X	X	X
ACQ-6	5.3.3	X	X	X	X	X		
Asthma exacerbation assessment	5.3.2	X	X	X	X	X	X	X
Adverse events	7.1	X	X	X	X	X	X	X
Concomitant medication	3.5	X	X	X	X	X	X	X
Serum chemistry	5.2.4	X			X	X	X	
Hematology	5.2.4	X			X	X	X	
Urinalysis	5.2.4	X			X	X	X	
Urine pregnancy test (dipstick) [b]	5.2.4.1	X	X	X	X	X	X	
PK	5.3.5	X		X	X	X	X	
ADA	5.3.7	X		X	X	X	X	
Serum antibodies to influenza virus				X[d]	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] For WOCBP only, urine HCG test to be done at center on each study visit (before IP administration on V3-5)

[c] In case of anaphylaxis additional samples to be taken (see Appendix F)

[d] Blood draw for serum antibodies to influenza vaccine should occur prior to administration of influenza vaccine.

[e] Influenza vaccine is to be administered at a different site than IP and site of injection noted. Patient is to be observed for 15 minutes after injection and before administering IP

ACQ-6 Asthma Control Questionnaire 6; ADA Anti-drug antibodies; ARE Antibody response evaluation; D Days; EOT End-of-treatment; FU Follow-up; IPD Premature investigational product discontinuation; PK Pharmacokinetics; UNSCH Unscheduled; V Visit; W Week

4.1 Enrollment and screening period

4.1.1 Enrollment (Visit 1)

Each potential patient will provide written informed consent/assent as appropriate with local guidance prior to any study specific procedures and undergo assessments applicable for the visit (see Table 1).

Informed Consent Form (ICF)/assent must also be obtained prior to any Visit 1 procedures and prior to instructing the patient to withhold any medication. Registration of patient's enrolment 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.

Pulmonary function tests and assessment of reversibility (maximum post-bronchodilator [post-BD] value of lung function) may be done if short- and long-acting bronchodilators have not been used for the patient as per Section 5.1.2.1.

Current, regular use of ICS prior to enrolment 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.

4.1.2 Screening (Visit 2)

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

Pulmonary function tests and assessment of reversibility (maximum post-BD value of lung function may be repeated at this visit, if pre-BD $FEV_1 \geq 50\%$ predicted and reversibility was not performed or achieved at Visit 1 and are needed to qualify the patient for randomization see Section 5.1.2.1).

4.1.3 Re-screening

Re-screening is allowed only once for the patient.

Re-screened patient/parent or legal guardian should re-sign informed consent/assent on the re-screening Visit 1. All procedures from the screening period should be repeated

4.1.3.1 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.

4.2 Randomized treatment period

Inclusion criteria at randomization will be confirmed at Week 0. Patients confirmed to be eligible will be randomised to either placebo or benralizumab 30 mg administered every 4 weeks throughout the treatment period.

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 asthma worsening/exacerbation (see Section 5.3.2), patients should be evaluated at the study center, when feasible.

Patients will receive 1 dose of seasonal influenza virus vaccine IM at Week 8. Samples for evaluation of antibody response will be drawn at Week 8 (prior to administration of the vaccine) and Week 12.

The End of Treatment (EOT) visit will be at Week 12, following the ARE assessments.

All patients who prematurely discontinue IP should return to the study center and complete the procedures described for the Premature IP Discontinuation (IPD) visit within 4 weeks±3 days.

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

4.3 Follow-up period

Patients who complete the double-blind randomized treatment period will be followed for 12 weeks after the last dose of IP for the Week 20 follow-up visit.

5. STUDY ASSESSMENTS AND TIMING OF PROCEDURES

5.1 Efficacy assessments

5.1.1 Humoral response to influenza vaccine

Serum HAI and MN antibody testing for antibody responses will be performed at Week 8 and Week 12. Methods for these analyses will be described in the laboratory manual.

5.1.2 Spirometry

General requirements

Lung function (reversibility, FEV_1 and FVC) at the study center will be measured by spirometry using the sites own equipment. Spirometry should be performed by the Investigator or

authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005).

Important! Patients should withhold their SABA medication(s) for at least 6 hours prior to Visit 2 (see Section 3.5.2.1). If Visits 1 and 2 are combined, bronchodilator therapy(ies) with or without ICS should be withheld for 12-24 hours depending on whether the patient is using twice- or once-daily bronchodilator-containing therapy.

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

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 value will be recorded using the local spirometer at the site with predicted values derived from the reference value of choice, eg, NHANES III 2010, Quanjer et al 2012, etc. 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-bronchodilator spirometry will be performed to satisfy reversibility inclusion criterion 8. The post-BD spirometry procedure should commence within 30±15 minutes according to the regimen for reversibility testing outlined in Section 5.1.2.1.

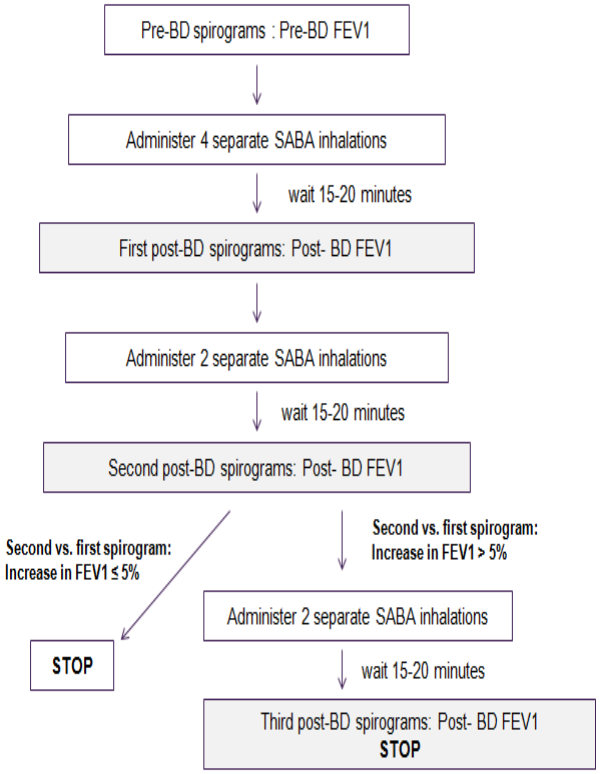
Order of administration of usual asthma controller medication and investigational product relative to scheduled pre- and post-bronchodilator spirograms

The patient's usual morning asthma controller therapy must not be given until after the initial pre-medication, pre-BD spirogram is complete for the reasons discussed above; usual asthma controller may be given after the post-BD spirogram.

5.1.2.1 Reversibility test and post-BD FEV_1 assessment

The procedure described in this section refers to the reversibility testing at Visit 1 or Visit 2. Bronchodilatation can be induced using albuterol (90 µg metered dose), salbutamol (100 µg metered dose) or levalbuterol (45 µg metered dose) up to a maximum of 8 inhalations). It is highly recommended to use a spacer device for this procedure. The algorithm for reversibility testing is outlined in Figure 2.

Figure 2 Reversibility testing algorithm



1 Verify with the patient that the medication restrictions to allow the reversibility assessment have been met (Section 3.5.2)

2 After a gentle and complete expiration, albuterol, salbutamol or levalbuterol is inhaled in one breath to TLC from a spacer device. The breath is then held for 5–10 seconds before the patient exhales. Four separate inhalations are delivered at approximately 30- second intervals. Post-BD spirometry should be performed 15-20 minutes later.

3 If the patient has not met reversibility criteria, an additional 2 inhalations of albuterol, salbutamol, or levalbuterol can be administered as single inhalations, 30 seconds apart (for a total of 6 inhalations). Second post-BD spirometry should be performed 15-20 minutes later.

4 If the patient still has not met reversibility criteria, an additional 2 inhalations of albuterol, salbutamol, or levalbuterol can be administered as single inhalations, 30 seconds apart (for a total of 8 inhalations). Second post-BD spirometry should be performed 15-20 minutes later.

A lower total dose, eg, 2 inhalations instead of 4 in the first round of puffscan be used if there is a concern about any effect on the patient's heart rate, tremor, or safety. The bronchodilator algorithm can be stopped at any time once a patient has met reversibility criteria.

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

Reversibility is calculated as follows:

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

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.

5.2 Safety assessments

5.2.1 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 7.1.

5.2.1.1 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.

5.2.1.2 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.

5.2.2 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.

Body temperature is to be recorded in degrees Celsius.

5.2.3 Local electrocardiogram

ECG are to be performed in accordance with the schedule provided in Table 1.

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).

A standard ECG with a recommended paper speed of 25 or 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.

It is highly recommended that the same machine is used for assessment throughout the patient's participation in the study.

ECG data and evaluation will be recorded in the eCRF.

5.2.4 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 significant in the Investigator's/authorized delegate's judgment should be reported as described in Section 7.1.3.

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 6.6).
[b] For patients on theophylline see Section 3.5.2.2.

5.2.4.1 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)
- 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.

5.3 Other assessments and procedures

5.3.1 Weight and height

Weight and height will be measured, and BMI calculated in accordance with schedules provided in Table 1 and Table 2.

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

5.3.2 Assessment of asthma exacerbations

In this study, an asthma exacerbation is defined by a worsening of asthma requiring the use of systemic corticosteroids (or an increase in oral steroid dose for those already on systemic corticosteroids) and/or an in-patient hospitalization, and/or an emergency department visit.

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

Asthma exacerbation information will be collected with a recall period of 'since the last scheduled visit'.

5.3.3 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).

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

The Investigator's clinical acumen and ACQ-6 results should be used in concert to determine whether or not the patient is well enough to continue in the current clinical study.

5.3.4 Other screening/run-in assessments

5.3.4.1 Serology

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

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

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

5.3.5 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 5 and 7, and the ARE/EOT, IPD and FU visits, 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 for repeat analysis of PK at AstraZeneca or designee for a maximum of 1 year following completion of the CSR.

5.3.6 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]).

5.3.7 Assessment of anti-benralizumab antibodies

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

The ADA samples will be retained for repeat analysis of ADA at AstraZeneca or a designee for a maximum of 1 year following completion of the CSR.

Serum will be collected pre-dose at Visit 3, as well as at Visit 5, Visit 7, and the ARE/EOT, IPD and FU visits, 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.

5.3.8 Handling of biological samples

5.3.8.1 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), see Appendix C 'IATA 6.2 Guidance Document'.

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.

5.3.8.2 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.

6. MANAGEMENT OF INVESTIGATIONAL PRODUCTS

6.1 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	Cook Pharmica LLC on behalf of MedImmune
Placebo	Matching placebo solution for injection in accessorized pre-filled syringe, 1 mL fill volume	Cook Pharmica LLC on behalf of MedImmune

6.2 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.

6.3 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).

The quadrivalent influenza vaccine used in this study should be stored and administered in accordance with the package insert.

6.4 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.

6.5 Methods for assigning treatment groups

Randomization codes will be assigned strictly sequentially in each stratum (adolescents [12-17 years of age] and young adults [18-21 years of age]) 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.

6.6 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.

6.7 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.

6.8 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 (benralizumab) and influenza vaccine will be administered at the study center on treatment visits and within visit windows as specified in Table 2.

Before IP administration

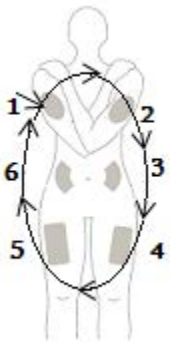
Prior to each IP administration and administration of influenza vaccine:

- Investigator/authorized delegate will assess injection sites as per standards of medical care
- For WOCBP, urine pregnancy test will be done; IP will be administered only when the result of the test is negative (see Section 5.2.4.1)

IP and influenza vaccine administration

The IP and influenza vaccine 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 3). At Week 8, the influenza vaccine should be injected at a site different than that of the IP injection site and should be administered prior to IP. The injection site(s) must be recorded in the source documents and the eCRF at each treatment visit.

Figure 3 Injection sites and rotation scheme



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

After influenza vaccine administration

After influenza virus administration, the patient should be observed for a minimum of 15 minutes for the appearance of any acute drug reaction and prior to administration of IP.

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

6.9 Management of investigational product-related reactions

Appropriate drugs (eg, epinephrine, H1 and H2 antihistamines, and corticosteroids), and medical equipment to treat acute anaphylactic reactions must be immediately available. Study personnel must be trained to recognize and treat anaphylaxis (Kroger et al 2011, Lieberman et al 2010). Management of anaphylaxis must be in accordance with current standard of care and clinical guidelines. Details on anaphylaxis management are provided in Appendix F.

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

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

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

3. Reduced blood pressure after exposure

Patients will have had a pre-assessment (ie, vital signs and lung function) prior to IP administration) and should be observed after IP administration for a minimum of 2 hours for the appearance of any acute drug reactions. Patients should also be observed in the clinic for 15 minutes after vaccine administration.

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

7. SAFETY REPORTING

7.1 Adverse events

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

7.1.1 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.

7.1.2 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 any of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix B.

7.1.3 Recording of adverse events

7.1.3.1 Time period for collection of adverse events

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

7.1.3.2 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.

7.1.3.3 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 7.1.2. 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.

7.1.3.4 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'.

A guide to the interpretation of the causality question is found in Appendix B.

7.1.3.5 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.

7.1.3.6 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.

7.1.3.7 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 7.1.2
- 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.

7.1.4 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. Refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

7.1.5 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 Web-based Data Capture (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.

7.2 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 7.1.5. For other overdoses, reporting should be done within 30 days.

7.3 Pregnancy

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

7.3.1 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 7.1.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

7.3.2 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.

8. EVALUATION AND CALCULATION OF VARIABLES

8.1 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

8.2 Sample size estimate

The study will have an estimated sample size of 50 patients in each treatment group. No formal statistical hypotheses will be tested. The sample size justification is based on the precision of the estimate of the GMTs (as $GMT_{vaccine}$ / $GMT_{benralizumab+vaccine}$). With 50 patients per arm, the 90% CI for the GMT ratio would be 0.67 to 1.48, assuming an observed ratio of 1, and that the log (post-dose HAI antibody titer or post-dose MN antibody titer) is normally distributed with a standard deviation (SD) of 1.2 on the natural log scale (Langley et al 2013). No formal statistical hypotheses will be tested.

8.3 Definitions of analysis sets

Antibody endpoints to the influenza vaccine—strain-specific HAI and MN antibody GMFRs and GMTs—will be analyzed using the vaccine immunogenicity analysis set. All remaining 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 and ADA will be analyzed based on the Safety analysis set.

8.3.1 All patients analysis set

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

8.3.2 Full analysis set

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

8.3.3 Vaccine immunogenicity analysis set

The vaccine immunogenicity analysis set will include all randomized subjects who received at least 1 dose of planned IP (ie, 1 dose of influenza vaccine, and plus 1 dose of benralizumab or placebo), had pre- and post-dose HAI and MN antibody measurements, and had no protocol deviation judged to have the potential to interfere with the generation or interpretation of an antibody response. The analyses conducted using this analysis set will be based on the actual treatment received. Protocol deviations will be reviewed by the study team before unblinding.

8.3.4 Safety analysis set

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

8.3.5 Pharmacokinetic analysis set

All patients who received benralizumab and from whom PK blood samples 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.

8.4 Variables for analyses

8.4.1 Calculation or derivation of efficacy variables

All efficacy objectives will be evaluated for the double-blind treatment period, defined as the period after administration of randomized IP at Week 0 and the conclusion of Week 12 (EOT) visit, inclusive.

8.4.1.1 Humoral immune response following seasonal influenza virus vaccination

The benralizumab versus placebo humoral immune responses following seasonal influenza virus vaccination will be assessed by

Primary objective:

- Post-dose strain-specific HAI antibody geometric mean folder rises (GMFRs) from Week 8
- Post-dose strain-specific HAI antibody geometric mean titers (GMTs) obtained at Week 12
- Proportion of patients who experience a strain-specific post-dose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in HAI antibody titer from Week 8
- Proportion of patients who achieve a strain-specific post-dose HAI antibody titer ≥40 at Week 12

Secondary objectives:

- Proportion of patients who achieve a strain-specific post-dose HAI antibody titer ≥320 at Week 12
- Post-dose strain-specific microneutralization (MN) antibody GMFRs from Week 8
- Post-dose strain-specific serum MN antibody GMTs obtained at Week 12
- Proportion of patients who experience a strain-specific post-dose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in MN antibody titer from Week 8

8.4.2 Calculation or derivation of safety variable(s)

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.

8.4.3 Calculation or derivation of patient reported outcome variables

8.4.3.1 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 categorized according to the following limits (Juniper et al 2005):

- 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

8.4.4 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.

8.4.5 Calculation or derivation of benralizumab immunogenicity variables

ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer).

8.5 Methods for statistical analyses

The analysis of the efficacy endpoints will include all data captured during the 16-week treatment period, including follow-up (where applicable), unless the patient or their parent/legal guardian withdraws consent/assent 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.

8.5.1 Analysis methods for antibody endpoints

Geometric mean fold rises for the HAI and MN antibody measurements are defined as:

$GMFR = \text{antilog}_z (\text{mean} [\log_z x])$

Where x is the post-dose HAI or MN antibody titer fold rise from Week 8 and z is the natural logarithm.

Geometric mean titers for the HAI and MN antibody measurements are defined as:

$GMT=antilog_z$ (mean [log_z y])

Where y is the HAI or MN antibody titer and z is the natural logarithm.

The analysis of the antibody endpoints—strain-specific GMFRs and GMTs—will be performed on the vaccine immunogenicity analysis set. GMFRs and GMTs will be summarized by treatment group. For GMFR and GMT, the geometric least square mean ratio between treatment groups (placebo/benralizumab) will be calculated via an ANCOVA model on the log-transformed variable, adjusting for treatment group. The least square geometric mean ratio will be provided with associated 90% CI.

Antibody response is defined as a ≥4-fold rise in HAI or MN antibody from Week 8. The proportion of patients who experience a post-dose antibody response at Week 12 and corresponding 90% Clopper-Pearson exact CI will be summarized by treatment group.

The proportion of subjects who achieve a post-dose HAI antibody titer ≥40 at Week 12 and corresponding 90% Clopper-Pearson exact CI will be summarised by treatment group.

The proportion of patients who achieve a post-dose HAI antibody titer ≥320 at Week 12 and corresponding 90% Clopper-Pearson exact CI will be summarized by treatment group.

No interim blinded review is planned.

8.5.2 Analysis methods for non-immunogenicity endpoints

Change from baseline in ACQ-6 score will be summarized by timepoint. ACQ-6 asthma control responder status will be summarized at Week 12 (EOT) by treatment group according to the following limits:

- ACQ-6 (EOT) ≤0.75 → Well controlled
- 0.75< ACQ-6 (EOT) <1.5 → Partly controlled
- ACQ-6 (EOT) ≥1.5 → Not well controlled

All analyses will be based on the full analysis set.

8.5.3 Analysis methods for safety variables

8.5.3.1 Asthma exacerbations

The number of asthma exacerbations and total follow-up time will be presented for each treatment group. This analysis will be based on the safety analysis set.

8.5.3.2 Other safety variables

AEs will be summarized by means of counts by study period (on-study, on-treatment, and follow-up period). AEs will be listed for each patient and summarised by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by MedDRA.

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 by endpoint and frequencies of clinically noteworthy values will also be presented. Shifts from normal to abnormal between baseline and follow-up will be evaluated for the physical examination.

8.5.3.3 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.

8.5.3.4 Analysis method for benralizumab immunogenicity variables

Anti-drug antibodies (ADA) to benralizumab will be summarized using descriptive statistics at each visit by treatment group.

8.5.4 Interim analysis

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

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 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, PROs, and other systems to be utilised.

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).

9.2 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/assent 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.

9.2.1 Source data

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

9.2.2 Recording of data

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

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

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

9.2.3 Study agreements

The 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 or designated CRO and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.4 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

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

The study is expected to start in Q3 2016 and to end by Q1 2017.

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.

9.4 Data management by AstraZeneca

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

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at Quintiles.

The Inform 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.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Patient data protection

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

10.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final study protocol, including the final version of the ICF/assent 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 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 or designated CRO 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/assent 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/assent is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca or designated CRO 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 or designated CRO will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 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/assent needs to be adjusted as per local requirements.
- Ensure each patient, parent, or legal guardian is notified that they are free to discontinue from the study at any time.
- Ensure that each patient, parent, or legal guardian is given the opportunity to ask questions and allowed time to consider the information provided.

- Ensure each patient, parent, 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/Assent 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.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International coordinating Investigator and AstraZeneca or designated CRO.

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 or designated CRO will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to EC see Section 10.3.

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

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

10.6 Audits and inspections

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.

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Clinical Study Protocol Appendix B

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Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

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

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

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

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

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

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

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

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

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

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix C	
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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

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

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Clinical Study Protocol Appendix D

Drug Substance	Benralizumab (MEDI-563)
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Appendix D
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

TABLE OF CONTENTS PAGE

1. INTRODUCTION

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

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP) (FDA Guidance 2009).

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

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥ 3x ULN **and** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

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

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

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

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

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

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

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

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

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

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

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

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

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

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

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

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

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

6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

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

At the first on study treatment occurrence of PHL criteria being, even if there has been no significant change the patient's condition[#] compared with pre-study treatment visits, the Investigator will:

- Notify the AstraZeneca representative who will inform the central Study Team.
- Follow the subsequent process described is Section 4.2 of this Appendix.

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

7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

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

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

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

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease << or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 6 >>?

If No: follow the process described in Section 4.2 of this Appendix

If Yes:

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

- If there is no significant change no action is required

- If there is a significant change follow the process described in Section 4.2 of this Appendix

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

8. REFERENCES

FDA Guidance 2009
Food and Drug Administration Guidance for Industry: Drug-induced liver injury: Premarketing clinical evaluation. US Department of Health and Human Services, FDA Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, July 2009.

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Clinical Study Protocol Appendix E	
Drug Substance	Benralizumab (MEDI-563)
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Appendix E
Background Therapy Equivalence Table

Estimated daily dosage for inhaled corticosteroids *

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

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Clinical Study Protocol Appendix F

Drug Substance	Benralizumab (MEDI-563)
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Appendix F
Anaphylaxis: signs and symptoms, management

1. INTRODUCTION

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

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

2. CLINICAL CRITERIA FOR DEFINING ANAPHYLAXIS AND IMMUNE COMPLEX DISEASE

Anaphylaxis

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

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

   AND AT LEAST ONE OF THE FOLLOWING

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

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

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

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

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

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

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

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

Immune Complex Disease

Immune complex disease or Hypersensitivity Type III is evoked by the deposition of antigen-antibody or antigen-antibody-complement complexes on cell surfaces, with subsequent involvement of breakdown products of complement, platelets, and polymorphonuclear leukocytes, and development of vasculitis; serum sickness and nephritis is common.

3. SIGNS AND SYMPTOMS AND MANAGEMENT OF ACUTE ANAPHYLAXIS

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

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

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles
- Rhinorrhea
- Change in voice
- Metallic taste
- Nausea, vomiting, diarrhea, abdominal cramps and bloating

- Lightheadedness
- Headache
- Uterine cramps
- Generalized warmth

4. MANAGEMENT OF ACUTE ANAPHYLAXIS

4.1 Immediate intervention

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

4.2 Possibly appropriate, subsequent measures depending on response to epinephrine

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

(b) Establish and maintain airway.

(c) Administer oxygen.

(d) Establish venous access.

(e) Normal saline IV for fluid replacement.

4.3 Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion.

(b) Consider H1 and H2 antihistamines.

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

(d) Consider systemic corticosteroids.

(e) Consider vasopressor (e.g. dopamine).

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

(g) Consider atropine for symptomatic bradycardia.

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

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

Adapted from Kemp et al 2008.

5. REFERENCES

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

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

Appendix G
Restricted and prohibited medications

PROHIBITED AND RESTRICTED MEDICATIONS

Medication restrictions

Table 1

Medication	Prohibited/restricted	Details
Live Attenuated Vaccines	Prohibited	Not allowed 30 days prior to randomization; during treatment period, and 16 weeks (5 half-lives) after the last dose of IP.
Influenza vaccine	Restricted	Receipt of an influenza vaccine within 90 days prior to randomization or during the study period (except for influenza vaccine at V5 per protocol).
Inactive/killed vaccinations (not applicable for inactive influenza vaccine)	Restricted	Allowed provided they are not administered within within 1 week before/after any IP administration.
Any immunomodulators or immunosuppressives	Prohibited	Not allowed within 3 months prior to the date informed consent is obtained.; during treatment period; 3 months or 5 half-lives (whichever is longer) after last dose of IP.
Blood products or immunoglobulin therapy	Prohibited	Not allowed 30 days prior to date of ICF, and during treatment period.
Any marketed (eg omalizumab) or investigational biologic treatment	Prohibited	Not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1; during treatment period; 4 months or 5 half-lives (whichever is longer) after the last dose of the investigational product
Other investigational products (including investigational use of an approved drug)	Prohibited	Not allowed 30 Days or 5 Half Lives (whichever is longer) prior to Visit 1, or during treatment period.
Allergen Immunotherapy	Restricted	Allowed if on stable therapy for at least 30 days prior to date of ICF; no anticipated changed during treatment. period.