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**Clinical Study Protocol**

Drug Substance	Benralizumab (Medi-563)
Study Code	D3250C00031
Version	1.0
Date	23 August 2016

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**A Multicenter, Open-label, Functionality, Reliability and Performance Study of a Single-use Auto-injector with Home-administered Subcutaneous Benralizumab in Adult Patients with Severe Asthma (GRECO)**

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Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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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.

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Drug Substance Benralizumab (Medi-563)  
Study Code D3250C00031  
Version 1.0  
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## VERSION HISTORY

<b>Version 1.0, 23 August 2016</b>
Initial creation

## PROTOCOL SYNOPSIS

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### **A Multicenter, Open-label, Functionality, Reliability and Performance Study of a Single-use Auto-injector with Home-administered Subcutaneous Benralizumab in Adult Patients with Severe Asthma (GRECO)**

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#### **International Coordinating Investigator:**

Redacted

#### **Study sites(s) and number of subjects planned:**

This study will be conducted in North America in approximately 30 study centers. Approximately 120 patients will enter the treatment phase of the study.

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<b>Study period</b>	<b>Phase of development</b>	
Estimated date of first subject enrolled	Q4 2016	Phase 3b
Estimated date of last subject completed	Q4 2017	

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## Study design

This is a multicenter, open-label study designed to assess patient- or caregiver-reported functionality, performance, and reliability of a single-use auto-injector (AI) with a fixed 30 mg dose of benralizumab administered subcutaneously (SC) in an at-home setting.

Approximately 120 adult patients with severe asthma will enter the treatment period to receive 5 subcutaneous doses (Week 0, Week 4, Week 8, Week 12, and Week 16) of benralizumab.

Following a 2 week screening period, eligible patients will receive 3 SC doses of 30 mg of benralizumab at the study site (Week 0, Week 4, and Week 8). At Week 0, the Principal Investigator or his/her designee will administer the study drug. At Week 4, the patient or caregiver will have the option of administering the study drug under study site supervision to ensure they understand the procedure and are capable of doing so. At Week 8, the patient or caregiver will have to perform the injection, again under site staff supervision. Patients or caregivers unable or unwilling to administer investigational product (IP) at this visit will be discontinued from the study.

The patient or caregiver will be given the Instructions for Use (IFU) to refer to for home administrations. The final 2 doses of benralizumab (Week 12 and Week 16) will be self-administered by the patient or administered by the caregiver at home. After each of these administrations, the patient will return for a scheduled on-site visit within 48 hours.

For the at-home administrations, whether the patient is self-administering or the caregiver is administering to a patient, the person administering the dose will fill out an administration questionnaire designed to indicate whether the device functioned correctly and the dose was successfully administered. Both the completed questionnaire and the used device are to be returned to the site during each of the clinic visits (Visit 5 and Visit 6). The site is to subsequently return the used devices and completed questionnaires to the Sponsor for evaluation.

An end-of-treatment (EOT) visit will be performed at Week 20 and a follow-up visit at Week 28 (12 weeks after last IP administration).

## Objectives

Primary objective	Outcome measure
To assess patient- or caregiver-reported functionality and reliability of the benralizumab single-use auto-injector (AI) in an at-home setting and performance of the AI device after use.	<ul style="list-style-type: none"> <li>• Proportion of patients/caregivers who successfully administered benralizumab 30 mg subcutaneously (SC) by injection with an AI device at home</li> <li>• Proportion of returned AI devices used to administer benralizumab at home that have been evaluated as functional</li> <li>• Proportion of AI devices used to administer benralizumab at home or in the clinic and have been reported as malfunctioning (Product Complaints)</li> </ul>

Secondary objectives	Outcome measure
To monitor metrics of asthma control	<ul style="list-style-type: none"> <li>• Change from baseline in mean Asthma Control Questionnaire-6 (ACQ-6) score</li> </ul>
To evaluate the pharmacokinetics, pharmacodynamics, and immunogenicity of benralizumab	<ul style="list-style-type: none"> <li>• Pharmacokinetic parameters</li> <li>• Peripheral blood eosinophil levels</li> <li>• Anti-drug antibodies (ADA)</li> </ul>

Safety objectives	Outcome measure
To assess the safety and tolerability of benralizumab	<ul style="list-style-type: none"> <li>• Adverse events (AEs) and serious adverse events (SAEs)</li> <li>• Laboratory variables</li> <li>• Physical examination</li> </ul>

## **Target subject population**

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

## **Investigational product, dosage and mode of administration**

Benralizumab 30 mg/mL solution for injection in a single-use auto-injector (AI) will be administered at the study center subcutaneously every 4 weeks for 3 doses (Week 0, Week 4, and Week 8) and then at-home every 4 weeks for 2 doses (Week 12 and Week 16).

## **Duration of treatment**

Following enrollment, the patient will enter a 2-week screening period, followed by a 20 week treatment period. A follow-up visit will be conducted at Week 28.

The total planned study duration is a maximum of 30 weeks.

## **Statistical methods**

The primary endpoints are the proportion of patients/caregivers who successfully administered benralizumab with an AI at home, the proportion of returned AIs used to administer benralizumab at home that have been evaluated as functional, and the proportion of AIs used to administer benralizumab at home or at the clinic and have been reported as malfunctioning (Product Complaints). Additional variables include the proportion of patient/caregivers who successfully administered benralizumab with an AI at both home administrations and the proportion of patients/caregivers who have returned AIs used to administer benralizumab at home that have been evaluated as functional at both times. All these endpoints will be presented using descriptive statistics and exact 95% confidence interval (CI) estimates. The estimated sample size recruitment of 120 patients is based upon a targeted recruitment and successful enrollment of 100 patients plus an adjustment to account for an assumed patient dropout rate of approximately 17% (20 patients); therefore, no hypotheses will be tested statistically and the endpoints and safety results will be summarized descriptively and all data will be listed.

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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.

<b>Abbreviation or special term</b>	<b>Explanation</b>
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
AI	Auto-Injector
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
Beta-hCG	Beta- human chorionic gonadotropin
BUN	Blood urea nitrogen
CI	Confidence interval
CO <sub>2</sub>	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency department
EOT	End of treatment
FEV <sub>1</sub>	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
GMP	Good Manufacturing Practice
HCP	Health care provider
HIV	Human immunodeficiency virus

<b>Abbreviation or special term</b>	<b>Explanation</b>
IATA	International Air Transport Association
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
Ig	Immunoglobulin
IL	Interleukin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-5R $\alpha$	Interleukin-5 receptor alpha subunit
IP	Investigational product
IPD	Premature IP Discontinuation
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-acting $\beta_2$ agonists
LTRA	Leukotriene receptor antagonists
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralizing antibody
OAE	Other significant adverse event
PK	Pharmacokinetic(s)
PRO	Patient reported outcome
RBC	Red blood cell
SABA	Short-acting $\beta_2$ agonists
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SUSARs	Suspected Unexpected Serious Adverse Reactions
ULN	Upper limit of normal
UNS	Unscheduled
WBC	White blood cell
WBDC	Web-based Data Capture
WOCBP	Women of childbearing potential

## **1. INTRODUCTION**

### **1.1 Background**

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

The current approach to anti-inflammatory controller therapy in asthma is based on a step-wise intensification of a daily maintenance regimen primarily centered around inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA), with the addition of long-acting  $\beta_2$  agonists (LABA) in patients with more severe asthma (GINA 2016, NAEPP 2007). Despite treatment per management guidelines, up to 50% of patients have asthma that is not well-controlled (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). Benralizumab (MEDI-563) is a humanized, afucosylated, monoclonal antibody that binds specifically to the human IL-5 receptor alpha subunit (IL-5R $\alpha$ ) on the target cell. The IL-5 receptor (IL-5R) is expressed almost exclusively on the surface of eosinophils and basophils (Takatsu et al 1994; Toba et al 1999). Afucosylation confers enhanced antibody-dependent cellular cytotoxicity (ADCC) which results in highly efficient eosinophil depletion by apoptosis (Kolbeck et al 2012). Single and repeated doses of benralizumab in mild to severe asthma patients has resulted in depletion of blood and airway eosinophils (Busse et al 2010, Gossage et al 2012, Molfino et al 2012). Also, a recent dose finding trial in severe asthma proved benralizumab to have benefit across a range of asthma outcomes including reductions in asthma exacerbations, improvements in lung function, and reduction in symptoms (Castro et al 2014).

The efficacy and safety of benralizumab has been confirmed in two large phase 3 trials, 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. (Bleecker et al 2016, FitzGerald et al 2016). The dose studied in these trials was 30 mg, a dose derived from pharmacokinetic/pharmacodynamic (PK/PD) modelling of the Phase 2 dose finding study, administered in 2 dosing regimens – either 30 mg every 4 weeks (Q4W) or 30 mg every 4 weeks (Q4W) for the first 3 doses followed by dosing every 8 weeks (Q8W) thereafter. The primary endpoint in each study was the annual rate of asthma-related exacerbations with key secondary endpoints being FEV<sub>1</sub> and asthma symptoms as defined by a daily patient diary.

The purpose of this study is to assess patient-or caregiver-reported functionality, performance, and reliability of a single-use auto-injector device used to administer a fixed 30 mg dose of benralizumab subcutaneously (SC) in an at-home setting.

## **1.2 Rationale for study design, doses, and control groups**

This is a multicenter open-label functionality, reliability and performance study of a single-use auto-injector with benralizumab. The primary endpoints will be the proportion of patients/caregivers who successfully administered benralizumab SC with an AI, the proportion of returned AI device used to administer benralizumab at home that have been evaluated as functional, and the proportion of AI device used to administer benralizumab at home or at the clinic and have been reported as malfunctioning (Product Complaints).

The benralizumab dose (30 mg SC, fixed) is based on population exposure-response modeling, and stochastic trial simulations from earlier benralizumab trials. The dosing regimen chosen, every 4 weeks (Q4W), is used in the pivotal Phase 3 efficacy and safety studies. Other stable asthma therapies on top of inhaled corticosteroids/long-acting  $\beta_2$  agonists (ICS/LABA) that are within expert guidance and that are not restricted per protocol (see Section 3.5.2) are allowed in order to accommodate local standards of care.

## **1.3 Benefit/risk and ethical assessment**

Benralizumab is primarily being studied in severe asthma where there are few treatment options for patients whose asthma remains uncontrolled on high dose ICS/LABA and oral corticosteroids (GINA 2016). In adult patients whose asthma was poorly controlled on medium-to-high dose ICS/LABA therapy, benralizumab at doses of  $\geq 20$  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). These findings have subsequently been confirmed in two large Phase 3 studies (Bleecker et al 2016, FitzGerald et al 2016) where a fixed dose of 30 mg was given either Q4W or Q8W.

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

with untreated parasitic infection and active or recent malignancy, in conjunction with the performance of routine pharmacovigilance activities.

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

The purpose of this trial is to confirm the successful use of benralizumab in an AI in an at-home setting by the patient or caregiver. A detailed assessment of injection site reactions and the overall risk/benefit of benralizumab in patients with asthma is given in the Investigator's Brochure (IB).

## **1.4 Study design**

This is a multicenter, open-label study designed to assess patient- or caregiver-reported functionality, performance, and reliability of a single-use auto-injector (AI) with a fixed 30 mg dose of benralizumab administered subcutaneously (SC) in an at-home setting.

Approximately 120 adult patients with severe asthma will enter the treatment period to receive 5 subcutaneous doses (Week 0, Week 4, Week 8, Week 12, and Week 16) of benralizumab.

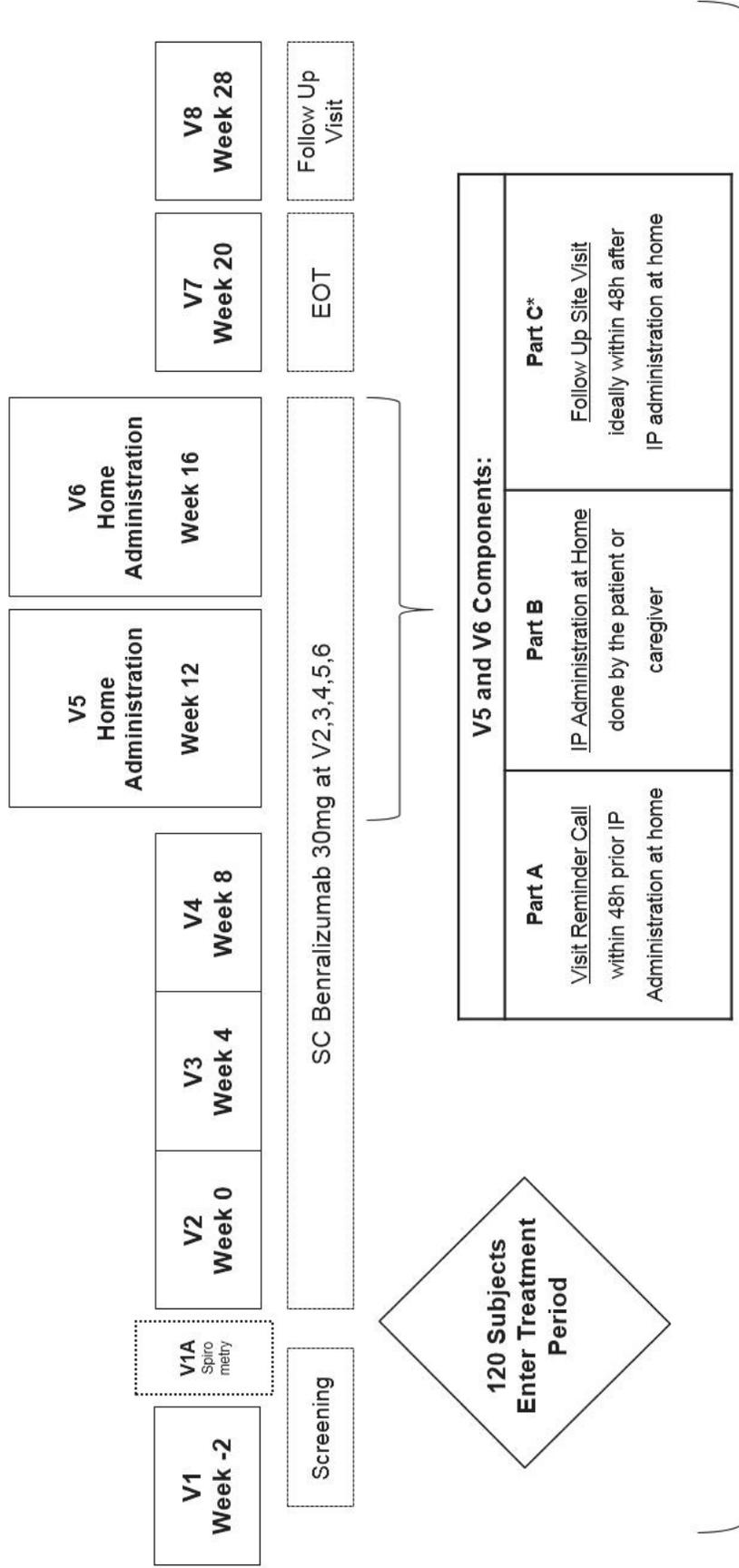
Following a 2 week screening period, eligible patients will receive 3 SC doses of 30 mg of benralizumab at the study site (Week 0, Week 4, and Week 8) (Figure 1). At Week 0, the Principal Investigator or his/her designee will administer the study drug. At Week 4, the patient or caregiver will have the option of administering the study drug under study site supervision to ensure they understand the procedure and are capable of doing so. At Week 8, the patient or caregiver will have to perform the injection, again under site staff supervision. Patients or caregivers unable or unwilling to administer investigational product (IP) at this visit will be discontinued from the study.

The patient or caregiver will be given the Instructions for Use (IFU) to refer to for home administrations. The final 2 doses of benralizumab (Week 12 and Week 16) will be self-administered by the patient or administered by the caregiver at home. After each of these administrations, the patient will return for a scheduled on-site visit within 48 hours.

For the at-home administrations, whether the patient is self-administering or the caregiver is administering to a patient, the person administering the dose will fill out an administration questionnaire designed to indicate whether the device functioned correctly and the dose was successfully administered. Both the completed questionnaire and the used device are to be returned to the site during each of the clinic visits (Visit 5 and Visit 6). The site is to subsequently return the used devices and completed questionnaires to the Sponsor for evaluation.

An end-of-treatment (EOT) visit will be performed at Week 20 and a follow-up visit at Week 28 (12 weeks after last IP administration).

**Figure 1** Study flow chart



Sponsor recommends to perform the at home IP administration during study center working hours in case of any questions or issues

\*Patient is to return used AI with administration questionnaire completed to the Study Site

## 2. STUDY OBJECTIVES

### 2.1 Primary objective

Primary objective	Outcome measure
To assess patient- or caregiver-reported functionality and reliability of the benralizumab single-use auto-injector (AI) device in an at-home setting and performance of the AI device after use.	<ul style="list-style-type: none"> <li>• Proportion of patients/caregivers who successfully administered benralizumab 30 mg subcutaneously (SC) by injection with an AI device at home</li> <li>• Proportion of returned AI devices used to administer benralizumab at home that have been evaluated as functional</li> <li>• Proportion of AI device used to administer benralizumab at home or in the clinic and have been reported as malfunctioning (Product Complaints)</li> </ul>

### 2.2 Secondary objectives

Secondary objectives	Outcome measure
To monitor metrics of asthma control	<ul style="list-style-type: none"> <li>• Change from baseline in mean Asthma Control Questionnaire-6 (ACQ-6) score</li> </ul>
To evaluate the pharmacokinetics, pharmacodynamics, and immunogenicity of benralizumab	<ul style="list-style-type: none"> <li>• Pharmacokinetic parameters</li> <li>• Peripheral blood eosinophil levels</li> <li>• Anti-drug antibodies (ADA)</li> </ul>

### 2.3 Safety objective

Safety objectives	Outcome measure
To assess the safety and tolerability of benralizumab	<ul style="list-style-type: none"> <li>• Adverse events (AEs) and serious adverse events (SAEs)</li> <li>• Laboratory variables</li> <li>• Physical examination</li> </ul>

### **3. SUBJECT SELECTION, ENROLMENT, TREATMENT, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL**

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

#### **3.1 Inclusion criteria**

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

1. Written informed consent for study participation must be obtained prior to any study related procedures being performed and according to international guidelines and/or applicable European Union (EU) guidelines.
2. Male and female patients aged 18 to 75 years of age at the time of Visit 1.
3. Patient or caregiver must be willing and able to administer the IP. Caregiver must be age of consent or older at the time of Visit 1, if applicable.
4. 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 vasectomised sexual partner, Implanon<sup>®</sup>, female sterilization by tubal occlusion, any effective IUD Intrauterine device/IUS Ievonorgestrel Intrauterine system, Depo-Provera<sup>™</sup> injections, oral contraceptive, and Evra Patch<sup>™</sup> or Nuvaring<sup>™</sup>. WOCBP must agree to use birth control, as defined above, from enrollment, throughout the study duration and until 16 weeks after last dose of investigational product (IP). WOCBP must also have negative serum pregnancy test result on Visit 1.

Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for 12 months prior to the planned date of Visit 2 without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years old are considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels in the postmenopausal range
  - Women ≥50 years old are considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment
5. 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

6. Weight of  $\geq 40$  kg
7. Evidence of asthma as documented by airway reversibility ( $FEV_1 \geq 12\%$  and 200 ml) demonstrated at Visit 1 or 1A or Visit 2  

If patients do not demonstrate airway reversibility at either Visit 1 or 1A or Visit 2 the patient must not enter the treatment period and must be rescreened, if appropriate. If re-screened, the study center should reiterate the need to withhold short- and long-acting bronchodilators as required in Section 5.1.1 prior to spirometry visits in an effort to meet this inclusion criterion. Visit 1A is optional for additional measurements if patient is on bronchodilators at the time of Visit 1.
8. 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  $\mu\text{g}/\text{day}$  fluticasone propionate dry powder formulation or equivalent daily. Equivalents for fluticasone dry powder can be found in Appendix F.
  - 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 (e.g., LTRAs, tiotropium, theophylline, oral corticosteroids) are allowed (see Section 3.5.2.1 for restricted therapies)
9. Pre-bronchodilator (pre-BD)  $FEV_1$  of  $>50\%$  predicted normal at Visit 1 or 1A or Visit 2
10. Not well-controlled asthma as documented by either
  - An ACQ6  $\geq 1.5$  OR
  - A peak expiratory flow of 60-80% predicted normal OR
  - One or more exacerbation that required oral or systemic corticosteroids in the previous year

### **Inclusion criteria at start of Treatment Period**

11. For WOCBP only: Have a negative urine pregnancy test prior to administration of the IP at day of Visit 2 (Week 0)

### **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, chronic obstructive pulmonary disease (COPD), bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated

- peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome)
2. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:
    - Affect the safety of the patient throughout the study
    - Influence the findings of the studies or their interpretations
    - Impede the patient’s ability to complete the entire duration of study
  3. Known history of allergy or reaction to the IP formulation
  4. History of anaphylaxis to any biologic therapy
  5. History of Guillain-Barré syndrome
  6. A helminth parasitic infection diagnosed within 24 weeks prior to the date informed consent is obtained that has not been treated with, or has failed to respond to standard of care therapy
  7. Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the screening
  8. Any clinically significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry, or urinalysis during screening period, which in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient’s ability to complete entire duration of the study
  9. Any clinically significant cardiac disease or any electrocardiogram (ECG) abnormality obtained during the screening/run-in period, which in the opinion of the Investigator may put the patient at risk or interfere with study assessments
  10. History of alcohol or drug abuse within 12 months prior to the date informed consent is obtained
  11. Positive hepatitis B surface antigen, or hepatitis C virus antibody serology, or a positive medical history for hepatitis B or C. Patients with a history of hepatitis B vaccination without history of hepatitis B are allowed to enroll
  12. A history of known immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test

13. Current smokers or former smokers with a smoking history of  $\geq 10$  pack years. A former smoker is defined as a patient who quit smoking at least 6 months prior to Visit 1.
14. History of cancer:
  - Patients who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained
  - Patients who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained
15. Use of immunosuppressive medication (including but not limited to: oral corticosteroid [for reasons other than asthma], methotrexate, troleandomycin, cyclosporine, azathioprine, 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.
16. Current use of an oral or ophthalmic non-selective  $\beta$ -adrenergic antagonist (eg, propranolol)
17. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level  $\geq 1.5$  times the upper limit of normal (ULN) confirmed during screening period.
18. Five- lipoxygenase inhibitors (eg, Zileuton) and roflumilast are prohibited.
19. Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent is obtained.
20. Receipt of any marketed (eg, omalizumab, mepolizumab etc) or investigational biologic within 4 months or 5 half-lives prior to the date informed consent is obtained, whichever is longer
21. Receipt of live attenuated vaccines 30 days prior to the date of Visit 2 (Week 0)
  - Receipt of inactive/killed vaccinations (eg, inactive influenza) is allowed provided they are not administered within 1 week before/after any investigational product administration.
22. Receipt of any investigational non-biologic within 30 days or 5 half-lives prior to Visit 2 whichever is longer
23. Previously received benralizumab (MEDI-563)
24. Initiation of new allergen immunotherapy is not allowed within 30 days prior to the date of informed consent. Immunotherapy initiated prior to this period or as a routine part of

the patient's seasonal treatment is allowed. If the immunotherapy is delivered as an injection, there should be a gap of 7 days between the immunotherapy and IP administration.

25. Planned surgical procedures during the conduct of the study
26. Currently breastfeeding or lactating women
27. Concurrent enrollment in another drug-related interventional clinical trial or post-authorization safety study (PASS)
28. AstraZeneca staff involved in the planning and/or conduct of the study
29. Employees of the study center or any other individuals involved with the conduct of the study, or immediate family members of such individuals

### **3.3 Subject enrolment and treatment**

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.

The Investigator will:

1. Obtain signed informed consent from the potential patient and caregiver if applicable, 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

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

Specific information concerning the use of the IWRS/IVRS will be provided in the separate manual.

### **3.4 Procedures for handling incorrectly enrolled patients**

Patients who fail to meet the eligibility criteria should not, under any circumstances, 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 initiated on treatment, and must be withdrawn from the study.

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

### **3.5 Concomitant medications, restrictions during and after the study**

#### **3.5.1 Concomitant medication**

Information about any treatment in the 3 months prior to the date of the informed consent and all the concomitant treatments given during the study with reason for the treatment will be collected by the Investigator/authorized delegate at each visit (as shown in Table 1 and Table 2) and recorded in the electronic Case Report Form (eCRF).

**Note:** To satisfy inclusion criterion 8 (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 may be increased from Visit 2 through 8 at the discretion of the Investigator to improve the patient's asthma control, if needed. If the addition of a new asthma controller therapy or a change in dose of any asthma medication(s) is judged by the Investigator as necessary, the justification should be documented in the source and in the eCRF.

A step down in therapy is discouraged and must be discussed beforehand with the AstraZeneca Study Physician.

##### **3.5.1.2 Rescue medication**

Short-acting bronchodilators (SABAs) may be used as rescue medication during the study.

The patient is to be prescribed an epinephrine-containing device (eg, EpiPen®) for use in the event of an allergic reaction and trained by the study center on its use (see Table 2). If a caregiver is administering the IP, the caregiver must also be trained on its use.

#### **3.5.2 Restrictions**

##### **3.5.2.1 Asthma medication restrictions**

- (a) **Use of long-acting beta-agonists as a reliever** (eg, Symbicort Maintenance and Reliever Treatment) is not allowed from enrollment and throughout the study duration
- (b) **Use of short-acting anticholinergics** (eg, ipratropium) as a rescue treatment for worsening asthma symptoms is not allowed from enrolment and throughout the study duration.

- (c) **Use of short-acting beta-agonists**

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

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

Any and all changes to the patient's background medication should be recorded in an eCRF and documented in source records along with a rationale for the change.

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

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

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

**Visit 1 or 1A or 2:** Patients should withhold their usual ICS-LABA medications on the day(s) when reversibility testing is being performed.

Twice daily ICS and LABA therapies should be withheld for 12-24 hours; once daily therapies containing ICS, LABA, or LAMA therapies should be withheld for  $\geq 24$  hours for eligibility assessment. In addition, SABA should not be used within 6 hours of these spirometry assessments. The patient's usual asthma medications may be administered following completion of the 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. Please see Section 3.2 exclusion criterion 15 for examples and further details.
- (b) Receipt of live attenuated vaccines within 30 days prior to Visit 2, 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 on the same day as the IP administration
- (d) When enrolling a patient who is on theophylline, digoxin, 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:
  - Five-lipoxygenase inhibitors (eg, Zileuton)
  - Roflumilast
  - Oral or ophthalmic non-selective  $\beta$ -adrenergic antagonist (eg, propranolol).

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

### **3.5.2.3 Other restrictions**

- (a) Fertile and sexually active patients or their partners should use highly effective contraceptive methods throughout the study and at least for 16 weeks (5 half-lives) after last administration of the IP. Male patients should refrain from fathering child or donating sperm from the time of informed consent, and for 16 weeks (5 half-lives) after last dose of IP (see Section 3.1, inclusion criteria 4 and 5; and Section 7.6)
- (b) Patients must abstain from donating blood or plasma from the time of informed consent and for 16 weeks (5 half-lives) after the last dose of IP.

### **3.6 Discontinuation of 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 to further treatment.
2. Adverse event (AE) that, in the opinion of the Investigator, contraindicates further dosing
3. Risk to patient as judged by the Investigator or AstraZeneca
4. Severe non-compliance to study protocol
5. Eligibility requirement found not to be fulfilled (see Section 3.4)
6. Pregnancy
7. Lost to follow-up<sup>1</sup>
8. Development of any study specific criteria for discontinuation:
  1. Anaphylactic reaction to the IP requiring administration of epinephrine
  2. Development of helminth parasitic infestations requiring hospitalization
  3. An asthma-related event requiring mechanical ventilation.
9. A patient who is self-administering IP who becomes unwilling or unable to continue to self-administer must be discontinued. Similarly, if a caregiver is giving the IP and becomes unwilling or unable to continue to administer IP to a patient, then that patient must be discontinued.

All patients who prematurely discontinue IP should return to the study center and complete the procedures described for the Premature IP Discontinuation (IPD) visit after 4 weeks ( $\pm 3$  days) and

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

the procedures for the Follow-up visit after 12 weeks ( $\pm 3$ days) of the last IP administration. The reason(s) for premature discontinuation of IP should be recorded in the eCRF.

### **3.7 Criteria for withdrawal**

#### **3.7.1 Screen failures**

Screen failures are patients who do not fulfill the eligibility criteria for the study and therefore must not enter the treatment part of the study. 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 patients in the treatment phase).

#### **3.7.2 Withdrawal of the informed consent**

Patients or caregivers, if applicable, are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment.

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

The enrollment code of the withdrawn patient cannot be reused. Withdrawn subjects will not be replaced.

#### **3.7.3 Discontinuation of the study**

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

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

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

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

#### 4. STUDY PLAN AND TIMING OF PROCEDURES

**Table 1 Study Plan – Enrollment, screening period**

Assessment/ activity	Refer to	Screening	
		V1 (W -2)	V1A <sup>d</sup> (V1 + max. 3 days)
Informed consent	10.4	X	
Inclusion/exclusion criteria	3.1/3.2	X	
Medical and asthma history	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	
Local ECG	5.2.3	X	
Serum chemistry	5.2.4	X	
Hematology	5.2.4	X	
Urinalysis	5.2.4	X	
Blood concentration (digoxin, theophylline) <sup>a</sup>	3.5.2.2	X	
Serology (hepatitis B,C; HIV-1; HIV-2)	5.3.3.1	X	
Serum pregnancy test	5.2.4.1	X	
FSH <sup>b</sup>	5.2.4.1	X	
Adverse events	7.1	X	
Concomitant medication	3.5	X	
ACQ-6 at Study Center	5.3.2.1	X	
Pre- and post-bronchodilator spirometry <sup>c</sup>	5.1.1	X	X <sup>d</sup>
Review of the AI IFU and the Administration Questionnaire	6.6	X	
Training on epinephrine-containing device	3.5.1.2	X	

<sup>a</sup> If and when appropriate prior to treatment period; for patients who are on theophylline or digoxin, (see Section 3.5.2.2)

<sup>b</sup> FSH test done only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 month

<sup>c</sup> Pre- and post-bronchodilator spirometry can be done at Visit 1 ( or optional Visit 1A<sup>d</sup>) OR Visit 2

<sup>d</sup> Visit 1A is optional for spirometry measurement only



**Table 2** Study Plan – Treatment period and follow-up

Assessment/ activity	Refer to	Treatment								EOT	IPD	FU	Unsch
		V2	V3	V4	V5	V6	V7	W16	W20				
		W0	W4	W8	W12	W28							
Visit window (days) <sup>a</sup>													
		±3	±3	±3	±3 <sup>h</sup>	±3 <sup>h</sup>	±3	±3	±3	±3	±3	±3	N/A
Adverse events	7.1	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	3.5	X	X	X	X	X	X	X	X	X	X	X	X
IP Administration at site <sup>g</sup>	6.6	X <sup>d</sup>	X <sup>e</sup>	X <sup>e</sup>									
IP Administration at home <sup>g</sup>	6.6				X <sup>e</sup>	X <sup>e</sup>							
Visit Reminder Call <sup>f</sup>	6.6				X	X							
Return of AI and admin. questionnaire	6.5				X	X							

<sup>a</sup> All visits are to be scheduled from the date of Visit 2 but not from the date of previous visit except in the case of early discontinuation from IP (see Section 3.6 for details).

<sup>b</sup> At those Visits training/review with the patient is optional.

<sup>c</sup> For WOCBP only, a urine HCG test must be done prior to IP administration at Visits 2 (Week 0), 3 (Week 4), and 4 (Week 8) at the study center. At-home urine pregnancy tests are to be done by WOCBP prior to IP administration at Weeks 12 and 16 and repeated by the center staff at Visits 5 and 6. In the case of a positive test, the patient is NOT to administer IP and is to call the study center. Urine pregnancy tests will be done at the study center at the EOT visit (Visit 7, Week 20) and the Follow-up visit (Visit 8, Week 28).

<sup>d</sup> Study drug will be administered on site by HCP in either the arm, thigh, or abdomen

<sup>e</sup> At Visit 3, the patient/caregiver has the option to administer the study drug. At Visits 4, 5, and 6, the patient/caregiver must administer the study drug. If self-administered by the patient, the study drug can be given in the thigh or abdomen. If administered by the caregiver, the sites of injection are in the upper arm, thigh, or abdomen

<sup>f</sup> Study center to perform visit reminder call to the patient within 48 prior scheduled home administration date for V5 & V6

<sup>g</sup> In case of anaphylaxis, additional samples to be taken (see Section 6.7 and Appendix D)

<sup>h</sup> The±3 day window is related to the IP administration at home and not the clinic visit, which should occur no later than 48h after IP administration

<sup>i</sup> Pre- and post-bronchodilator spirometry can be done at Visit 1 (optional Visit 1A) OR Visit 2.

<sup>j</sup> Neutralizing antibody (nAb) testing will occur for all samples that are ADA positive. Samples that are ADA negative will not be tested for nAb.

**\* pre-dose sample**

EOT End-of-treatment; FU Follow-up; HCG Human chorionic gonadotropin; HCP Healthcare provider; IFU Instructions for Use; V Visit; W Week

## **4.1 Enrollment and screening period**

### **4.1.1 Enrollment (Visit 1)**

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

Patients (and caregiver, if applicable) must sign the Informed Consent Form (ICF) prior to any Visit 1 procedures. Registration of the patient's enrollment via IWRS/IVRS should occur on day when other Visit 1 procedures are done. The auto-injector IFU, epinephrine containing device and administration questionnaire will be reviewed as part of the informed consenting process.

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

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

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

### **4.1.2 Re-screening**

Re-screening is allowed only once for any patient.

Re-screened patients should re-sign the informed consent on the re-screening Visit 1. All Visit 1 procedures should be repeated.

#### **4.1.2.1 Procedures for patients who experience an exacerbation during screening**

Patients who experience an asthma exacerbation during screening should be treated according to local medical practice.

## **4.2 Treatment period**

Inclusion criteria will be confirmed at Visit 2 (Week 0). Eligible patients will receive 5 doses of benralizumab 30 mg every 4 weeks (Q4W).

Following a 2 week screening period, eligible patients will receive 3 SC doses of benralizumab at the study center (Week 0, Week 4, and Week 8). The first injection of IP will be done at the study center by the HCP at Visit 2 (Week 0). At the Visit 3 (Week 4) and Visit 4 (Week 8) administrations, the patient or caregiver will be asked to administer the study drug themselves under study center supervision to ensure they understand the procedure and are capable of doing so. If the patient is not willing/able to self-administer (or the caregiver is not willing/able to administer) at Visit 4 (Week 8), the patient will be discontinued from IP. At Visit 4 (Week 8) after completion of a self-administration, the patient will be given: epinephrine containing device, IP along with the

Instructions for Use (IFU) and Administration Questionnaire to complete after home administration. The final 2 doses of benralizumab (Week 12 and Week 16) will then be administered by the patient or a caregiver at home. After each of these administrations, the patient will return for a scheduled on-site visit within 48 hours.

The AI Administration Questionnaire (please see Appendix G) is to be filled out by the patient (if self-administering) or by the caregiver (if they administered the IP to the patient). That person will fill out a questionnaire designed to indicate whether the device functioned correctly and the dose was successfully administered. Both the administration questionnaire and the used device are to be returned to the study center during each of the clinic visits after at-home administration. Study Center Staff will instruct the patient or caregiver, if applicable, on how to complete the questionnaire and properly return the device.

For Visit 2 through Visit 4, all study procedures must be done on the scheduled day of IP injection. Urine pregnancy tests must be done prior to IP administration at Visits 2 (Week 0), 3 (Week 4), and 4 (Week 8). At-home urine pregnancy tests are to be done by WOCBP prior to IP administration at Weeks 12 and 16 and repeated by the study center staff at Visits 5 and 6. In the case of a positive test, the patient is NOT to administer IP and is to call the study center. Urine pregnancy tests will be done at the study center at the EOT visit (Week 20) and the Follow-up visit (Week 28).

The same person must administer the IP during the entire study, whether it is the patient or caregiver.

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 7.3.7), patients should be evaluated at the study center when feasible.

Patients will return to the study center at Week 20 for the EOT visit and at Week 28 for a Follow-up visit. If the IP was administered by a caregiver, the caregiver must accompany the patient to these visits.

For premature discontinuation please refer to Section 3.6.

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 treatment period will be followed for 12 weeks after the last dose of IP for the Follow Up visit (Week 28).

## **5. STUDY ASSESSMENTS**

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

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

## **5.1 Efficacy assessments**

### **5.1.1 Spirometry**

#### **General requirements**

Lung function (reversibility, FEV<sub>1</sub> and FVC) at the study center will be measured by spirometry using the study centers own equipment. Spirometry will be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005).

The Principal Investigator or authorized delegate is responsible for assuring that the spirometer is in a good working condition, calibrated and meets ATS/ERS recommendations and that the study center personnel who will be performing the testing are properly certified.

Patients should withhold their SABA medication(s) for at least 6 hours prior to spirometry (see Section 3.5.2.1). LABA therapy (with or without ICS) should be withheld for 12-24 depending on whether the patient is using twice or once daily LABA-containing therapy, respectively.

#### **Time for scheduled centre visit spirometry**

Spirometry testing should be done according to the schedule provided in Table 1 and Table 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. 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.

The forced expiratory maneuvers (FEV<sub>1</sub> 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, or 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 1 best effort (highest FEV<sub>1</sub>) that meet the ATS/ERS acceptability and reproducibility criteria will be recorded in the eCRF. The absolute measurement (for FEV<sub>1</sub> and FVC), and the percentage of predicted normal value will be recorded. The best effort values will be based on the one with highest FEV<sub>1</sub>.

### 5.1.1.1 Reversibility test and post-BD FEV<sub>1</sub> assessment

The procedure described in this section refers to the reversibility testing at Visit 1 or optional 1A 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 4 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.

**Pre-BD spirometry: Pre-BD FEV<sub>1</sub>**



**Administer up to 4 separate SABA inhalations**



**Post-BD spirometry: Post-BD FEV<sub>1</sub>**

Four separate inhalations are delivered at approximately 30- second intervals. Post-BD spirometry should be performed 30-60 minutes later.

- 3 If the patient still has not met reversibility criteria at Visit 1 further attempts to demonstrate reversibility criteria are allowed at optional Visit 1A or Visit 2

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

Reversibility should be calculated as follows:

$$\% \text{ Reversibility} = \frac{\text{post-BD FEV}_1 - \text{pre BD FEV}_1}{\text{pre-BD FEV}_1} \times 100$$

#### Record keeping

A signed and dated copy of the spirometry printout must be kept at study center for source data verification. The printout must be marked with the study code, enrollment code, date and time of measurement, visit number. Recorded data will be entered into the eCRF.

### **5.1.2 Assessment of self and caregiver administration with the single-use auto-injector**

One of the primary endpoints of interest is the proportion of patients/caregivers who successfully administered benralizumab with the AI device at home. A successful administration is defined as an injection completed and an answer of “Yes” to all 5 questions in the administration questionnaire (please see Appendix G) and satisfactory in vitro evaluation of the returned devices.

### **5.1.3 Assessment of returned single-use auto-injector device through in vitro evaluation**

In addition to the administration questionnaire filled out and returned with each at-home administered dose, the used AI device will be returned to the Sponsor for in vitro evaluation. The data collected in the in vitro evaluation of the AI devices falls into 2 categories: 1) Visual inspection, and 2) Functional evaluation. The visual inspection will assess the returned devices for any visible damage or disassembly, full plunger travel indicating a complete dose was expelled, and needle guard deployment. The functional evaluation will challenge the needle safety guard to assess whether it deployed correctly and continued to provide protection against accidental needle stick injuries. As mentioned in Section 5.1.2, a satisfactory in vitro evaluation of the returned devices and a completed administration questionnaire with an answer of “Yes” to all 5 questions in the questionnaire will constitute a successful administration. Any device defects reported during the in vitro evaluation will result in a full product complaint investigation. In the event that the answers to one or more of the questions on the questionnaire indicate that the user was unable to complete a successful administration, an evaluation will be performed on the returned device. The evaluation will take into account information provided on the administration questionnaire. If the in vitro evaluation of the device shows no observable device defect, then the unsuccessful administration may be classified as a use error and not a device malfunction (e.g. user removes Autoinjector from the injection site before the injection is complete).

## **5.2 Safety assessments**

### **5.2.1 Physical examination**

Physical examination will be done in accordance with schedule 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 will include 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 will include 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**

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 will be measured in Celsius.

### **5.2.3 Electrocardiograms**

Electrocardiograms (ECGs) are to be performed in accordance with the schedule provided in Table 1. Measurements will be performed on local study center based equipment.

A 12-lead ECG will be taken in supine position after the patient has been resting for at least 5 minutes.

A standard ECG with a recommended paper speed of 50 mm/second covering at least 6 sequential beats should 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.

### **Record keeping**

A signed and dated copy of the ECG printout must be kept at study center for source data verification. The printout must be marked with the study code, enrollment code, date and time of measurement, visit number. ECG data and evaluation will be recorded in the eCRF.

### **5.2.4 Laboratory safety assessments**

Safety laboratory tests (list provided in Table 3 below) 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 the Table 1 and Table 2.

**Table 3 List of safety laboratory tests**

<b>Clinical chemistry (serum or plasma)</b>	<b>Haematology/Haemostasis (whole blood)</b>	<b>Urinalysis</b>
ALP (Alkaline phosphatase)	Hematocrit	Appearance
ALT (alanine aminotransferase)	Hemoglobin	Blood
AST (aspartate aminotransferase)	Mean corpuscular volume (MCV)	Color
Bilirubin, total	Platelet count	Glucose
BUN (blood urea nitrogen)		
Calcium	Red blood cell (RBC) count	Ketones
Chloride	WBC count with differential	Microscopy including WBC/high power field (HPF), RBC/HPF
Cholesterol, total		
CO <sub>2</sub> (carbon dioxide)		pH
Creatinine		Specific gravity
Gamma-GT (gamma-glutamyl transpeptidase)		
Glucose		
Phosphorus		
Potassium		
Sodium		
Uric acid		
Serum concentration <sup>a</sup>		

<sup>a</sup> For patients on theophylline or digoxin (see Section 3.5.2.2)

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 7.3

**NB.** In case a subject shows an AST **or** ALT  $\geq 3 \times \text{ULN}$  **and** total bilirubin  $\geq 2 \times \text{ULN}$  please refer to Appendix C ‘Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy’s Law’, for further instructions.

#### 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)
- FSH: To be done at screening Visit 1 only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for  $\geq 12$  months
- Urine HCG: To be performed at the study center for WOCBP at Visits 2, 3, and 4 before IP administration using a dipstick. The test will be performed at home prior to the 2 at-home IP administrations, and again at the study center at Visits 5, 6, 7, 8. 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 the BMI will be calculated, in accordance with schedules provided in Table 1.

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

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

#### **5.3.2 Patient-reported outcomes**

##### **5.3.2.1 Asthma Control Questionnaire (ACQ-6)**

The ACQ-6 is a shortened version of the ACQ that assesses asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and short-acting  $\beta_2$  agonist use) omitting the FEV<sub>1</sub> 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  $\leq 0.75$  indicate well-controlled asthma, scores between 0.75 and  $\leq 1.5$  indicate partly controlled asthma, and a score  $> 1.5$  indicates not well controlled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered to be clinically meaningful. The questionnaire will be completed at the study center in accordance with schedule provided in Table 1 and Table 2.

#### **5.3.3 Other screening assessments**

##### **5.3.3.1 Serology**

**Hepatitis B surface antigen, hepatitis C antibody:** To be done only at screening; test to be performed at central laboratory.

**HIV-1 and HIV-2 antibodies:** To be done only at screening; 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.

#### **5.3.4 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. Samples will be collected according to the schedule of study procedures.

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

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

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

#### **5.3.5 Pharmacodynamics**

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]).

#### **5.3.6 Immunogenicity**

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

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

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

#### **Anti-drug antibodies**

Serum samples for analysis of anti-drug antibodies (ADA) will be collected pre-dose at selected visits according to the study plan (see Table 2).

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

#### **Neutralizing antibodies**

Neutralizing antibodies (nAb) testing will occur on all samples that are ADA positive. Samples that are ADA-negative will not be tested for nAb.

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

#### **5.3.7 Pharmacogenetics**

Pharmacogenetic samples will not be taken during the study.

### **5.3.8 Biomarker analysis**

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

### **5.3.9 Handling of biological samples**

#### **5.3.9.1 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 B ‘ATA 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.

#### **5.3.9.2 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 (where applicable).

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 PRODUCT**

### **6.1 Identity of investigational product(s)**

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

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

**Table 4 Identity of investigational product**

<b>Investigational product</b>	<b>Dosage form and strength</b>	<b>Manufacturer</b>
Benralizumab	30 mg/mL solution for injection in the single-use auto-injector device, 1mL fill volume	MedImmune

## **6.2 Labeling**

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

The label will include the following information:

- study code
- Investigational product/study drug dosage form, route of administration and quantity of dosage units
- kit ID
- P Lot ID
- Expiry date
- Investigator Name (to be written on the label)
- E-code (to be written in the label)
- Sponsor name and contact details
- Directions for use
- Storage condition
- Standard statements required by regulatory authorities

## **6.3 Storage**

Benralizumab 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 while IP stored at study center.

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).

Patients can transport the IP in uncontrolled temperature conditions but should return it to a refrigerator as soon as possible. The temperature is not monitored during storage by the patient; standard refrigeration is sufficient to maintain appropriate temperatures while the IP is in the patient's possession.

In the following cases neither the center staff nor the patient or caregiver should use the affected IP and should immediately contact an AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study center
- Damaged kit upon receipt
- Damaged AI device

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

## **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 or return of materials to the Sponsor. Certificates of delivery, destruction, and/or return should be signed.

The patient will be responsible for refrigerating the product at home. The patient will be responsible for returning used AI devices and completed administration questionnaires to the study center.

**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.

## **6.5 Methods for return of used single-use auto-injector devices**

Study sites will be shipped an appropriate number of Bio-bottles (hard plastic, wide-mouth bottles approved for containing and shipping biohazardous and/or sharps materials). Patients who are given IP to administer at home will also be given one Bio-bottle for each of the two doses to be administered at home. The Bio-bottle will be given at the time the IP is provided to the patient.

Instruction for Use (IFU) provided to the patient with each IP kit will include instructions on how to properly package the used AI device in the Bio-bottle. Patients will be instructed to bring the used AI device packaged in the Bio-bottle along with the completed administration questionnaire to the clinic during next center visit.

The completed administration questionnaire and the Bio-bottle containing the used AI will be returned to the Sponsor by the clinical site following the Auto-injector Return Working Instruction document provided to the study sites. All site coordinators of clinical centers participating in the study will receive training prior to study start.

### **6.5.1 Reporting product complaints**

Any defects with the IP must be reported immediately to the Site Monitor. All defects will be communicated to the Sponsor and investigated further with the AstraZeneca Supply Chain Group. During the investigation of the product complaint, all IP must be stored at labeled conditions 2°C to 8°C (36°F to 46°F), separated from other IP kits, unless otherwise instructed.

### **6.5.1.1 Reporting defects**

Product defects may be related to component, product, or packaging and labeling issues prior to or during use. Product defects should be reported to the Study Monitor. The list below includes, but is not limited to, descriptions of product complaints in these 3 categories should be reported as defects:

- **Component Issue:** Defect in container or dosing mechanism of the IP. The component defect may be damaged, missing, or broken. Component examples include the Autoinjector and the prefilled syringe housed within the Autoinjector.
- **Product Issue:** Defect in the product itself. The product appearance has visual imperfections such as foreign particles, crystallization, discoloration, turbidity, insufficient volume, or anything that does not apply to the product description in the IFU.
- **Packaging/Labeling Issue:** Defect in the packaging or labeling of the product. The packaging (carton, thermo-fitted tray, or tamper-evident seal) or labeling defects may be damaged or unreadable, or the label may be missing.

### **6.5.1.2 Single Use Auto-Injector malfunction**

An AI device malfunction is when the AI device appears normal during verification of shipment and then does not work during administration, e.g., the autoinjector activated prematurely, the autoinjector stalled or did not expel the full volume, needle guard safety feature did not deploy or remain locked, glass syringe breakage, needle bent or broke upon use. Device malfunctions should be reported using the Device Malfunction Return Instruction and the Study Monitor should be notified.

Site staff will be asked to send back malfunctioning devices to the depot or local sponsor company according to local procedures. Address and attention for malfunctioning device is available in the Device Malfunction Return Instruction.

## **6.6 Investigational product administration and treatment compliance**

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the Case Report Form (CRF).

The IP will be administered at the study center for first 3 doses and at home for following 2 doses. IP administration should be done within visit windows as specified in

. All information regarding IP administration will be provided in the Instruction for Use (IFU).

### **Before investigational product administration**

Prior to each IP administration at study center:

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

Prior to each IP administration in at-home setting:

- Investigator/authorized delegate will perform visit reminder call within 48h prior scheduled IP administration. The conversation should include only basic information and serve as a reminder to the patient about the next scheduled visit to occur within 48 hours after home administration.
- 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)

### **Investigational product administration**

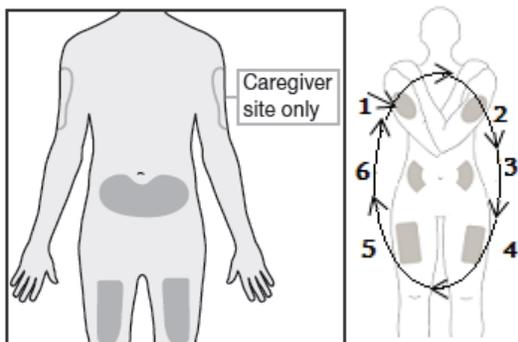
The IP will be administered by the Investigator/authorized delegate/patient/caregiver as specified in Table 2. If patient is not willing or not able to self-administer (or caregiver is not willing/able to administer) at Visit 4 patient will be discontinued from the IP.

It is suggested that the site of injection of the IP be rotated such that the patient receives IP at a different anatomical site each time. Suggested injection site rotation sequence is presented below (see Figure 3). In the case when rotation of the injection site is not favorable for the patient and/or Investigator, the reason should be recorded in the source documents. The injection site must be recorded in the source documents and the eCRF at each treatment visit.

If IP is self-administered by the patient, the injection should be done in the abdomen or thigh; when the injection is performed by the healthcare provider (HCP) or caregiver: in the abdomen, or thigh or upper arm (site reserved only for injections performed by HCP or caregiver - see Figure 3). The same person must administer the IP throughout the study, whether it is the patient or caregiver.

Further details on IP administration are provided in the Instruction for Use (IFU). Investigational product administration must be carried out in line with the instructions provided.

**Figure 3** Injection sites and rotation scheme



### **After investigational product administration**

After IP administration the patient should be observed for a minimum of 2 hours by the HCP (or responsible adult if injection was done at home) for the appearance of any acute drug reactions. Patient/caregiver will be trained by the study site on the use of epinephrine containing device that will be provided. If IP administration was performed at home, the patient should visit the study centre for the previously scheduled center visit within 48 hours after IP administration.

### **Conditions requiring investigational product administration rescheduling**

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

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

The patient and caregiver, if applicable, should be informed about these conditions and reminded prior to at-home administration. In case of any doubts before at-home administration, patient should contact study center.

## **6.7 Management of investigational product-related reactions**

Prior to the first 3 administrations, which will be performed in the clinic, patients will have had a pre-assessment (ie, vital signs) prior to IP administration, and will be observed after IP administration for a minimum of 2 hours for the appearance of any acute drug reactions.

Study personnel should inform patients that, for subsequent administrations, they should be observed for 2 hours after IP administration for the appearance of any acute drug reactions. As with any medication, in case of an anaphylactic reaction at home, the patient or caregiver should immediately contact an emergency care unit or emergency transportation as per standard medical practice, and contact study site personnel.

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

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:

10. 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
11. 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
12. Reduced blood pressure after exposure

In order to help understand the potential drug-relatedness of any acute reaction, a blood sample should be drawn during the event for 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 AND MEDICAL MANAGEMENT**

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

### **7.1 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.

### **7.2 Definitions of serious adverse event**

A serious adverse event (SAE) is an AE occurring during any study phase (ie, 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 1 of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A to the Clinical Study Protocol

## **7.3 Recording of adverse events**

### **7.3.1 Time period for collection of adverse events**

Adverse events will be collected from the time the patient signs the informed consent, throughout the treatment period and including the follow-up period (through Week 28).

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

### **7.3.2 Follow-up of unresolved adverse events**

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

### **7.3.3 Variables**

The following variables will be collect for each AE;

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

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 7.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 7.2.

#### **7.3.4 Causality collection**

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

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

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

#### **7.3.5 Adverse events based on signs and symptoms**

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: ‘Have you had any health problems since the previous visit/you were last asked?’, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or

symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

### **7.3.6 Adverse events based on examinations and tests**

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

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

### **7.3.7 Disease progression**

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

- The sign or symptom is serious according to definition, see Section 7.2
- The patient discontinues the study due to the sign or symptom.
- The sign or symptom is new to the patient or is not consistent with the patient's pre-existing asthma history as judged by the Investigator.

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

### **7.3.8 Hy's Law**

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

## **7.4 Reporting of serious adverse events**

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

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

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

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

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

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

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

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

## 7.5 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 7.4 For other overdoses, reporting should be done within 30 days.

## **7.6 Pregnancy**

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

### **7.6.1 Maternal exposure**

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

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 7.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

### **7.6.2 Paternal exposure**

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

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

## **8. STATISTICAL ANALYSES BY ASTRAZENECA**

### **8.1 Statistical considerations**

Analyses will be performed by AstraZeneca or its representatives.

The SAP will be prepared prior to first patient enter treatment period and any subsequent amendments will be documented, with final amendments completed prior to data base lock

## **8.2 Sample size estimate**

No hypotheses will be tested statistically. Approximately 120 patients will receive the treatment to allow approximately 100 patients to complete the study. It is based upon a targeted recruitment with an adjustment to account for a 17% patient's drop-out rate.

## **8.3 Definitions of analysis sets**

Three patient populations are defined below: All patients' analysis set, Full analysis set (FAS), and Pharmacokinetics analysis set.

Patients must have provided their informed consent. If no signed informed consent is collected (major protocol deviation (PD)), then the patient will be excluded from all analysis sets defined below.

### **8.3.1 All patients analysis set**

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

### **8.3.2 Full analysis set**

All patients receiving at least one IP will be included in the full analysis set (FAS), irrespective of their protocol adherence and continued participation in the study. Patients who withdraw consent to participate in the study will be included up to the date of their study termination.

All analyses, except for PK analysis, will be performed using the FAS.

### **8.3.3 Pharmacokinetic analysis set**

All patients who received benralizumab and from whom PK blood samples were collected are assumed not to be affected by factors such as protocol violations will be included in the PK analysis dataset. 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 primary endpoints**

#### **8.4.1.1 Primary endpoints**

The primary endpoints are as follows:

- Proportion of patients/caregivers who successfully administered benralizumab with an AI device at home among those who have been deemed by the Principal Investigator to be suitable for at-home administration and are still in the study at Week 12 or Week 16. A successful administration is defined as an injection completed, an answer of

“Yes” to all 5 questions in the administration questionnaire (see Appendix G), and the autoinjector adequately passed the visual inspection and functional tests.

Patients/caregivers who are unwilling to self-administer at Week 8 will not be considered as failures, but will be counted as unsuitable for at-home administration and follow the premature IP Discontinuation (IPD) procedure.

- Proportion of returned AI devices used to administer benralizumab at home that have been evaluated as functional among all returned AI devices used to administer benralizumab at home. A functional AI device is defined as an answer of “Yes” to all the questions in the visual inspection and function tests. Devices that are not returned for evaluation will be excluded from analysis.
- Proportion of returned AI devices used to administer benralizumab at home and in the clinic that have been reported as malfunctioning (Product Complaints).

The first 2 endpoints above will be calculated at Weeks 12 and 16, while the third endpoint will be obtained at each of the post-treatment periods (Weeks 0, 4, 8, 12, and 16).

In addition, the following variables will be calculated among all patients/caregivers who have been deemed by the Investigator to be suitable for at-home administration at Week 8 and are still in the study at Week 16:

- Proportion of patients/caregivers who successfully administered benralizumab with an AI device at both Weeks 12 and 16, and
- Proportion of patients/caregivers who returned an AI device used to administer benralizumab at home and evaluated as functional at both Weeks 12 and 16.

#### **8.4.2 Calculation or derivation of efficacy variable(s)**

##### **8.4.2.1 Asthma Control Questionnaire (ACQ-6)**

The outcome variable for ACQ-6 will be the change in mean score from baseline (Week 0) to each of the post-treatment periods.

Patients will be categorized according to their asthma control responder status using the following limits (Juniper et al 2005) at the end of treatment (EOT) visit:

- $ACQ-6 \text{ (EOT - baseline)} \leq -0.5 \rightarrow \text{Improvement}$
- $-0.5 < ACQ-6 \text{ (EOT - baseline)} < 0.5 \rightarrow \text{No change}$
- $ACQ-6 \text{ (EOT - baseline)} \geq 0.5 \rightarrow \text{Deterioration}$

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

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

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

### **8.4.3 Calculation or derivation of safety variable(s)**

#### **8.4.3.1 Safety variables**

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

Change from baseline (Week 0) to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements.

#### **8.4.3.2 Other significant adverse events**

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

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

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

### **8.4.4 Calculation or derivation of pharmacokinetic variables**

No formal PK data analysis is planned due to the limited sampling schedule and variations in sampling time post self-administration. Benralizumab serum concentrations will be summarized at each visit using descriptive statistics. The PK results will be provided in the CSR.

### **8.4.5 Calculation or derivation of immunogenicity variables**

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

## **8.5 Methods for statistical analyses**

The analysis of the primary endpoints will include all data captured during Weeks 12 and 16 (for Product Complaints with addition of Weeks 0, 4 and 8) while secondary endpoints will include all data captured during the 20-week treatment period, and up to follow-up (where applicable), unless the patient withdraws consent to study participation, regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol

adherence. All efficacy analyses will be performed using an Intent-to-Treat (ITT) approach based on the FAS. For consistency, demographic and baseline characteristics will be presented using FAS. Safety objectives will also be analyzed using the FAS.

### **8.5.1 Primary and secondary analysis method(s)**

No formal statistical analyses will be performed. Primary and secondary endpoints will be summarized descriptively and all data will be listed. Exact 95% confidence interval estimates will also be presented for the primary endpoints.

#### **8.5.1.1 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. No formal PK data analysis is planned due to sparse sampling and variations of sampling time following benralizumab self-administrations. Observed serum concentrations of benralizumab for each individual will be listed by visit to confirm benralizumab administration. Serum concentrations of benralizumab will be provided in the CSR.

#### **8.5.1.2 Analysis methods for blood eosinophil levels**

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

#### **8.5.1.3 Analysis method for immunogenicity variables**

The potential association of ADA with safety will be evaluated. The association of ADA titer with benralizumab concentration and blood eosinophil levels will be evaluated for ADA-positive patients only.

### **8.5.2 Analysis methods for safety variables**

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

Laboratory 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. Similar summaries will be performed for vital signs. Shifts from normal to abnormal between baseline and follow-up will be evaluated for the physical examination.

### **8.5.3 Subgroup analysis**

To explore the uniformity of the estimates, the primary endpoints will also be summarized separately for patients self-administering and caregivers who are administering to the patient for the first 2 endpoints.

## **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 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 utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, study patient and caregiver if applicable, 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 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**

Please 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 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 Q4 2016 and to end by Q4 2017

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

## **9.4 Data management by AstraZeneca**

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

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

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

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

The data will be validated as defined in the data management plan (DMP). Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The DMP will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

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

### **Serious adverse event reconciliation**

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

### **Data associated with human biological samples**

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

## **10. ETHICAL AND REGULATORY REQUIREMENTS**

### **10.1 Ethical conduct of the study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on

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

## **10.2 Subject data protection**

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

## **10.3 Ethics and regulatory review**

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

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

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

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

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

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

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

AstraZeneca will provide Regulatory Authorities, ECs, and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the ECs/Institutional Review Board (IRB) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca 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 needs to be adjusted as per local requirements.

- Ensure each patient or legal guardian is notified that they are free to discontinue from the study at any time.
- Ensure that each patient or legal guardian is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient or legal guardian provides signed and dated Informed Consent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent(s) is/are stored in the Investigator's Study File and kept for a period that is compliant with GCP/local regulatory requirements, whichever is longer.
- Ensure a copy of the signed Informed Consent Form is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the Informed Consent Form that is approved by an Ethics Committee.

## **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.

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

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

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

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

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

## **10.6 Audits and inspections**

Authorised representatives of AstraZeneca, a regulatory authority, or an EC 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,

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analysed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonisation (ICH), 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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