AstraZeneca

Revised Clinical Study Protocol	
Drug Substance	Benralizumab (MEDI-563)
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A Multicenter, Open-label, Safety Extension Study with Benralizumab (MEDI-563) for Asthmatic Adults on Inhaled Corticosteroid Plus Long-acting β2 Agonist (MELTEMI)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative

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

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
1	18 July 2017		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change
1	17 February 2016		

PROTOCOL SYNOPSIS

A Multicenter, Open-label, Safety Extension Study with Benralizumab (MEDI-563) for Asthmatic Adults on Inhaled Corticosteroid Plus Long-acting β2 Agonist (MELTEMI)

International Co-ordinating Investigator

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Study center(s) and number of patients planned

This study will be conducted worldwide in approximately 300 centers. Approximately 1000 patients who have completed at least 16 weeks in Study D3250C00021 (BORA) on investigational product may be eligible for this study.

Study period		Phase of development
Estimated date of first patient enrolled	Q2/3 2016	Phase 3b
Estimated date of last patient completed	TBD	

Objectives

(a) Primary Objective

Objective	Endpoint
• To assess the safety and tolerability of 2 dosing regimens of benralizumab for adult patients	• AEs/SAEs • Laboratory assessments

(b) Secondary Objectives

Objective	Endpoint
• To evaluate the effect of 2 dosing regimens of benralizumab on asthma exacerbations, and asthma-related hospitalizations and emergency room visits	• Asthma exacerbations • Asthma-related hospitalizations and/or emergency room visits.
• To evaluate the pharmacodynamics and immunogenicity of 2 dosing regimens of benralizumab for adult patients	• Eosinophil levels • Anti-drug antibodies (ADA)

Study design

This is an open-label study designed to evaluate the safety and tolerability of benralizumab 30 mg administered subcutaneously (SC) for patients who complete at least 16 and not more than 40 weeks in Study D3250C00021. Patients who have completed 40 weeks or more in BORA will finish BORA to enable the objectives of that study to be met.

The 16-week treatment period in Study D3250C00021 (BORA) allows patients on placebo in the predecessor studies to receive at least the 3 monthly doses ("loading doses") of benralizumab within BORA before transition into this study and continuing with either the every 4 week (Q4W) or every 8 week (Q8W) dosing regimen.

Patients transitioning to Study D3250C00037 will need to complete Study D3250C00021 end of treatment (EOT) assessments and sign an informed consent for Study D3250C00037, after which their treatment allocation will be unblinded. Patients will then receive their first dose of benralizumab for Study D3250C00037and their subsequent visits will be scheduled accordingly. Patients on the Q4W regimen will attend study visits every 4 weeks; patients assigned to the Q8W regimen will attend study visits every 8 weeks.

Target patient population

Adult patients who complete at least 16 and not more than 40 weeks in Study D3250C00021.

Patients can remain in Study D3250C00021 if they choose not to enter Study D3250C00037.

Investigational product and mode of administration

Benralizumab 30 mg/mL solution for injection in an accessorized pre-filled syringe (APFS) will be administered SC at the study site according to the dosing regimens described below.

Dosage

Patients will remain on the same dosing regimen as they had received during the preceding D3250C00021 (BORA) study:

Patients previously randomized to the 4 week (Q4W) regimen of benralizumab in BORA will continue injections of active drug every 4 weeks in this open label study.

Patients previously randomized to the 8 week (Q8W) regimen in BORA will continue to receive active drug every 8 weeks in this open label study.

Duration of treatment

Patients may stay on IP until it is commercially available in their local market or the candidate drug is withdrawn from the approval process in their local market. If transitioned to commercialized product at that time, no follow up visit is needed. If the patient will not be transitioned to commercialized product, the patient should come in for the FU visit and complete the study. For countries in which a marketing application is not submitted, patients will receive their last dose of benralizumab in December 2018, with EOT and FU visits in 1Q 2019.

Statistical methods

A descriptive analysis based on the full analysis set will be performed for all endpoints. The full analysis set includes all enrolled patients who received any dose of IP.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
APFS	Accessorized pre-filled syringe
AST	Aspartate aminotransferase
Beta-hCG	Beta- human chorionic gonadotropin
BUN	Blood urea nitrogen
CO_2	Carbon dioxide
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
EU	European Union
FSH	Follicle-stimulating hormone
Gamma-GT	Gamma-glutamyl transpeptidase
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
IATA	International Air Transport Association
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
Ig	Immunoglobulin
IL	Interleukin

Abbreviation or special term	Explanation
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-5Rα	Interleukin-5 receptor alpha subunit
ICI	International Coordinating Investigator
IP	Investigational product
IPD	Premature Investigational Product Discontinuation
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-acting β_2 agonists
LTRA	Leukotriene receptor antagonists
MedDRA	Medical Dictionary for Regulatory Activities
NAEPP	National Asthma Education Prevention Program
OCS	Oral corticosteroids
PFS	Pre-filled syringe
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
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 stepwise intensification of a daily maintenance regimen primarily centered around inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA), with the addition of long-acting β_2 agonists (LABA) in patients with more severe asthma (GINA 2015, NAEPP 2007). Despite treatment per management guidelines, up to 50% of patients have asthma that is not well-controlled (Bateman et al 2010). This results in considerable impact on quality of life, disproportionate use of healthcare resources, and adverse reactions from regular systemic steroid use. Therefore, there remains an unmet medical need for patients whose asthma is not controlled by existing therapies.

The observed variability in clinical response to currently available asthma therapies appears to be related, in part, to distinctive inflammatory phenotypes (Wenzel 2012). In particular, asthma associated with eosinophilic inflammation in the airway (often referred to as eosinophilic asthma) is common (approximately 40% to 60% of asthmatics) with the degree of eosinophilia associated with clinical severity including the risk of asthma exacerbations (Bousquet et al 1990; Louis et al 2000; DiFranco et al 2003; Scott and Wardlaw 2006, Simpson et al 2006; Zhang and Wenzel 2007). Adjusting conventional ICS-based asthma therapy according to the degree of elevated sputum eosinophils as a marker of disease activity resulted in a reduction in the frequency of asthma exacerbations in prospective trials (Green et al 2002; Jayaram et al 2006).

Interleukin-5 (IL-5) is a cytokine factor essential for eosinophil trafficking and survival (Molfino et al 2011). Clinical trials of neutralizing anti-IL-5 antibodies (mepolizumab and reslizumab) in patients with uncontrolled eosinophilic asthma resulted in an improvement in key asthma control metrics, including asthma exacerbations (Castro et al 2011and Pavord et al 2012). These promising results support continued development of therapies targeting the IL-5 pathway in eosinophilic asthmatics unresponsive to standard therapies.

In contrast to anti-IL-5 therapies, benralizumab (MEDI-563) is a humanized, afucosylated, monoclonal antibody that binds specifically to the human IL-5 receptor alpha subunit (IL-5Rα) on the target cell. The IL-5 receptor (IL-5R) is expressed almost exclusively on the surface of eosinophils and basophils (Takatsu et al 1994; Toba et al 1999). Afucosylation confers enhanced antibody-dependent cellular cytotoxicity (ADCC) which results in highly efficient eosinophil depletion by apoptosis (Kolbeck et al 2012). Single and repeated doses of benralizumab in mild to severe asthma patients during Phase 2 development resulted in depletion of blood and airway eosinophils, and improvement in multiple metrics of asthma

control including asthma exacerbations, lung function, and Asthma Control Questionnaire (ACQ-6) scores (Busse et al 2010, Gossage et al 2012, Molfino et al 2012, and Phase 2b MI-CP220 study). For further details please refer to the Investigator's Brochure.

1.2 Rationale for conducting this study

The treatment options for patients who remain uncontrolled by ICS-LABA are limited. As such, patients with severe refractory asthma and an eosinophilic phenotype will be allowed to remain in this study and on investigational product (IP) until benralizumab is commercially available in their local market or the candidate drug is withdrawn from the approval process in that market.

In previous clinical studies, benralizumab administration resulted in rapid and prolonged depletion of eosinophils in the peripheral blood in the asthmatic airway with associated improvements in multiple metrics of asthma control. The purpose of this study is to continue to characterize the safety profile of benralizumab administration and monitor the pharmacodynamic activity of the drug in those asthma patients who remain on treatment for at least 16 weeks in the predecessor study D3250C00021 (BORA).

1.3 Rationale for study design, doses, and control groups

This is an open-label safety extension study designed to evaluate the safety and tolerability of a fixed 30 mg dose of benralizumab administered subcutaneously (SC) in severe asthma patients on ICS-LABA therapy with or without chronic oral corticosteroids (OCS) and/or other asthma controllers. All patients will receive active drug on the same dosing regimen they received in BORA. In order to protect the blind of BORA, patients will remain blinded to treatment regimen allocation until they have completed all EOT assessments in BORA and signed informed consent for participation in this study, after which treatment allocation will be unblinded to both the investigator and the patient.

1.4 Benefit/risk and ethical assessment

There are few treatment options for patients whose asthma remains uncontrolled on high-dose ICS-LABA (GINA 2015). The evidence base for oral add-on therapies (ie, oral corticosteroids, leukotriene inhibitors, and xanthenes) is extremely limited. Anti-IgE therapy (ie, omalizumab) may improve control in patients with severe asthma and IgE-mediated allergy to a perennial allergen. Tiotropium is a long-acting bronchodilator that has recently been shown to produce improvement in lung function and exacerbation risk (pooled data) in patients with severe asthma, with inconsistent effects on other measures of asthma control (Kerstjens et al 2012). As such, new therapies are needed for asthma management in patients who remain uncontrolled on standard of care.

In adult patients whose asthma was poorly controlled on medium-to-high dose ICS-LABA benralizumab, at fixed doses of ≥20 mg, produced improvements in multiple metrics of asthma control including the annual rate of asthma exacerbations, lung function, ACQ-6 scores, and symptoms (Phase 2b MI-CP220 study, based on the interim analysis). Clinical benefit appeared to be greatest in patients with blood eosinophil counts ≥300/μL. The blood

eosinophil count below which benralizumab is generally not effective remains unclear at this point in time.

An assessment of the risk/benefit of benralizumab in patients with asthma is provided in the Investigator's Brochure.

The efficacy and safety of benralizumab in asthmatic patients is being evaluated in studies D3250C00017 (SIROCCO), D3250C00018 (CALIMA), and D3250C00020 (ZONDA). Eligible patients who have completed the entire treatment period on investigational product in 1 of these studies may be allowed to enrol in Study D3250C00021 (BORA), a safety extension study.

Approximately 2200 patients are anticipated to enrol in BORA. The Sponsor believes that approximately 1200 patients completing BORA are sufficient to address the primary objectives of that study. As such, the remaining eligible BORA patients will be allowed to transition to Study D3250C00037 (MELTEMI) and have open-label access to study drug until benralizumab is commercially available in their local market or the candidate drug is withdrawn from the approval process in their local market. For countries in which a marketing application is not submitted, patients will receive their last dose of benralizumab in December 2018, with EOT and FU visits in Q1 2019.

1.5 Overall study design

This is an open-label safety extension study designed to provide continued treatment to patients who have completed preceding studies in this program. The study will evaluate the safety and tolerability of a fixed 30 mg dose of benralizumab administered subcutaneously (SC). Patients who complete at least 16 and not more than 40 weeks in the predecessor study may be eligible to enrol into this study. Patients will remain blinded to treatment regimen allocation until they have signed informed consent for participation in this study, after which treatment allocation will be unblinded to both the investigator and the patient.

Patients previously randomized to the every 4 weeks (Q4W) regimen of benralizumab in BORA will continue injections of active drug every 4 weeks in this open label study.

Patients previously randomized to the every 8 week (Q8W) regimen in BORA will continue to receive active drug every 8 weeks in this open label study.

Patients must remain on a medium- to high-dose ICS-LABA therapy, throughout the treatment period. Any changes in ICS-LABA therapies or other background therapies must be documented in the appropriate eCRF.

Patients will be allowed to remain in this study until benralizumab is commercially available in their local market or the candidate drug is withdrawn from the approval process in the local market. For countries in which a marketing application is not submitted, patients will receive their last dose of benralizumab in December 2018, with EOT and FU visits in Q1 2019..

The total patient population for this study will be approximately 1000 patients, comprising patients from Study D3250C00021.

2. STUDY OBJECTIVES

(a) Primary Objective

Objective	Endpoint
• To assess the safety and tolerability of 2 dosing regimens of benralizumab for adult patients	• AEs/SAEs • Laboratory assessments

(b) Secondary Objectives

Objective	Endpoint
• To evaluate the effect of 2 dosing regimens of benralizumab on asthma exacerbations, and asthma-related hospitalizations and emergency room visits	• Asthma exacerbations • Asthma-related hospitalizations and/or emergency room visits.
• To evaluate the pharmacodynamics and immunogenicity of 2 dosing regimens of benralizumab for adult patients	• Eosinophil levels • Anti-drug antibodies (ADA)

3. PATIENT SELECTION CRITERIA AND WITHDRAWAL CRITERIA

3.1 Inclusion criteria

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

1. 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 guidelines.

2. Female and male patients who have completed at least 16 and not more than 40 weeks in Study D3250C00021.

3. Women of childbearing potential (WOCBP) must agree to use an effective form of birth control throughout the study duration and for 16 weeks after the last dose of IP. Effective forms of birth control include: true sexual abstinence, a vasectomized sexual partner, Implanon, female sterilization by tubal occlusion, any effective IUD

Intrauterine device/IUS Ievonorgestrel Intrauterine system, Depo-Provera™ injections, oral contraceptive, and Nuvaring™. Women of childbearing potential (WOCBP) are defined as all females regardless of the onset of menarche who do not meet the definition below of women not of childbearing potential.

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

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

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

4. For WOCBP only: Have a negative urine pregnancy test prior to administration of IP at Visit 1.

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.

3.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

1. 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 study or their interpretations
   - Impede the patient's ability to complete the entire duration of study

2. A helminth parasitic infection diagnosed during a predecessor study that has either required hospitalization, has not been treated, has been incompletely treated or has failed to respond to standard of care therapy

3. Any clinically significant change in physical examination, vital signs, ECG, hematology, clinical chemistry, or urinalysis during the predecessor study 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 interfere with the patient's ability to complete the entire duration of the study

4. Current malignancy or malignancy that developed during the predecessor study (subjects that had basal cell carcinoma, localized squamous cell carcinoma of the skin which was resected for cure, or in situ carcinoma of the cervix that has been treated/cured will not be excluded).

5. Receipt of live attenuated vaccines within 30 days prior to initiation of treatment in this study, during the treatment period, and for 16 weeks (5 half-lives) after the last dose of the IP

6. Receipt of immunoglobulin or blood products within 30 days prior to Visit 1

7. Planned major surgical procedures during the conduct of the study

8. Previous participation in the present study

9. Concurrent enrolment in another drug-related interventional clinical trial

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

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

12. Patients with important protocol deviations in the predecessor study at the discretion of the Sponsor

13. Patients with ongoing serious adverse events (SAEs) from the prior study should not be enrolled into the this extension study until the SAE has resolved (see Section 7.1.3.1)

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

3.3 Patient enrolment

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Patients who are asked to transition into this study by the Investigator must do so at the next odd-numbered visit in BORA (ie, Visit 5, 7, 9, or 11) once this study has started at their site.

1. Patients must have completed at least 16 and not more than 40 weeks in BORA before transitioning into this study
2. Patients can transition to this study only on the following BORA visits: 5, 7, 9, or 11. Patients who do not transition into this study by Visit 11 of BORA will remain in BORA through EOT and FU.

3. Provide the patient with the ICF for this study

4. On the day of transition, the Investigator should:

   - Confirm patient eligibility based on Sections 3.1 and 3.2.

     NOTE: Patients with an ongoing SAE will **not** be allowed to transfer into this study until the SAE is resolved.
   - Perform all EOT assessments for BORA study
   - Obtain informed consent for this study before any study-related procedures are performed
   - Call IVRS to register completion of BORA, obtain unblinded treatment regimen allocation and IP kit number to dose the patient for this study at this visit (Patients will retain the same eCode as in BORA.)
   - Provide the patient with information on treatment regimen and schedule subsequent visits accordingly
   - Dose patient with IP from this study's supply, NOT from BORA supplies
   - Observe patient for a minimum of 2 hours for the appearance of any acute drug reaction
   - Record appropriate assessments in eCRF for both BORA (EOT) and this study (Visit 1)

5. Patients on the Q4W regimen will attend study visits every 4 weeks, patients assigned to the Q8W regimen will attend study visits every 8 weeks.

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

Where a patient does not meet all the eligibility criteria but is enrolled and treated in error, 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 on a case by case basis. 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

All concomitant treatments given during the study, including those which were started during BORA and are ongoing when the patients enters this study, will be collected by the Investigator/authorized delegate, with reason for treatment, at each visit (as shown in Table 1 and Table 2) and recorded in the eCRF.

3.5.1.1 Background medication

Patients must remain on a medium- to high-dose ICS-LABA therapy, throughout the treatment period. Any changes in ICS-LABA therapies or other background therapies must be documented in the appropriate eCRF.

Other asthma controller (eg, oral corticosteroids, long acting anti-muscarinics) and rescue use therapies are also allowed at the discretion of the Investigator. If changing asthma medication(s) is judged necessary during the course of the study, the justification should be documented in the source and the change of drugs and/or doses reflected in the eCRF.

3.5.2 Restrictions

3.5.2.1 Medication-related restrictions

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

3.5.2.2 Other restrictions

(a) Fertile and sexually active patients or their partners should use effective contraceptive methods throughout the study and for at least for 16 weeks (5 half-lives) after last administration of the IP. Male patients should refrain from fathering a child or donating sperm from the time of informed consent and for 16 weeks (5 half-lives) after last dose of IP (see Section 3.1, inclusion criteria 3, 4 and 5; Section 7.3.

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

3.6 Discontinuation from investigational product

Patients will be discontinued from IP in the following situations:

1. Patient decision. The patient is at any time free to discontinue treatment without prejudice to further treatment (see Section 3.7)
2. Adverse event (AE) that in the opinion of the Investigator or Sponsor contraindicates further dosing
3. Risk to patient as judged by the Investigator or AstraZeneca
4. Severe non-compliance to study protocol
5. Eligibility requirement found not to be fulfilled (see Section 3.4)

6. Worsening in asthma control as determined by the Investigator.
7. Pregnancy
8. Prior to conduct of any major surgical procedures. All surgical procedures should be discussed with the AZ physician before continuing IP in this study.
9. Lost to follow-up[1]
10. Development of any study specific criteria for discontinuation:
    (a) Anaphylactic reaction to the IP requiring administration of epinephrine
    (b) Development of helminth parasitic infestation requiring hospitalization
    (c) If 2 consecutive doses of IP missed. **NOTE:** For 8W regimen, in case one dose is skipped the next dose must be given within the visit window. If this is not possible the patient shall be discontinued.
    (d) An asthma-related event requiring mechanical ventilation

Reasons for premature discontinuation of IP should be recorded in the eCRF. Premature discontinuation of IP is defined for the purposes of this study as discontinuation of IP before it is commercially available in the local market, before the candidate drug is withdrawn from the approval process in the local market, or before the termination of this study.

3.7 Withdrawal from the study

3.7.1 Withdrawal of Informed Consent

Patients 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 adverse events (AE). The Investigator will follow up any ongoing AEs present at the time of withdrawal outside of the clinical study. The enrolment code of the withdrawn patient cannot be reused.

If the patient chooses to discontinue taking investigational product (no matter what is the cause of this decision) but agrees to return for the IPD and FU visits, then this is not considered a main consent withdrawal and data will continue to be collected.

The patient should then return to the study center and complete procedures described for the IPD and follow-up (FU) visits within 4 weeks (+7 days) and 12 weeks (±7 days) after the last dose of IP, respectively.

If the main informed consent is withdrawn, no further study data and samples may be collected.

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

3.8 Withdrawal of informed consent for donated biological samples

Samples taken for the evaluation of ADA will be retained for repeat analysis of ADA at AstraZeneca or designee for a maximum of 1 year following completion of the clinical study report (CSR). If a patient/parent or legal guardian withdraws consent to the use of blood samples, the samples will be disposed of/destroyed and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator or designee:

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

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

As use of the biological samples is an integral part of the study, withdrawal of informed consent for the use of donated samples by the patient will result in the patient being withdrawn from further study participation.

4. STUDY PLAN AND PROCEDURES

Table 1 Study Assessments Schedule – Q4W regimen – Year 1[a]

Assessment/ activity	Refer to	Treatment														**EOT[h]**	**IPD[i]**	**FU[h,i]**	**UNS[j]**
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14				
		w0	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48	w52	4 wks after last dose	4 wks after last dose	12 wks after last dose	
		Visit window (days)[c]																	
		±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	±7	N/A
Informed consent	10.4	X																	
Inclusion/exclusion criteria	3.1/3.2	X																	
Medical, surgical, and asthma history	4.1.1	X[b]																	
Hematology	5.2.1	X				X				X				X		X	X	X	
Serum chemistry	5.2.1	X												X		X	X	X	
Urine pregnancy test (dipstick)[d]	5.2.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
FSH[e]	5.2.1.1	X																	
Vital signs	5.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
ADA[f,g]	5.3.4	X				X				X				X		X	X	X	

Table 1 Study Assessments Schedule – Q4W regimen – Year 1[a]

Assessment/ activity	Refer to	Treatment														EOT[h]	IPD[i]	FU[h,i]	UNS[j]
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14				
		w0	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48	w52	4 wks after last dose	4 wks after last dose	12 wks after last dose	
		Visit window (days)[c]																	
		±0	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	±7	N/A
Assessment of asthma exacerbations and asthma-related HRU	5.3.1/5.3.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	7.1	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	3.5	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administration of IP[i]	6.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

[a] Visits and treatment to continue every 4 weeks until EOT. For Years 2, 3, and 4 (Week 56 [Visit 15] to Week 208 [Visit 53]), see Appendix G.
[b] Medical, surgical, and asthma history, concomitant medications, and ongoing AEs must be entered manually. Data will not be integrated from BORA.
[c] All visits are to be scheduled from the date of enrolment, not from the date of previous visit
[d] For WOCBP, urine HCG test to be done at center on each treatment visit before IP administration.
[e] FSH test done only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 months to confirm postmenopausal status..
[f] ADA samples to be collected before IP administration.
[g] In case of anaphylaxis additional samples to be taken (see Section 6.7)
[h] EOT visit will occur when benralizumab has been approved and is available in the local market or the candidate drug is withdrawn from the approval process in the local market. For countries in which a marketing application is not submitted, patients will receive their last dose of benralizumab in December 2018, with EOT and FU visits in 1Q 2019.
[i] IPD visit to be conducted on early discontinuation of IP (see Section 3.6). Patients who complete an IPD visit will return 8 weeks (±7 days) later, ie, 12 weeks after the last dose of IP, for a final follow-up visit.
j Perform any assessments considered clinically relevant.
D Days; EOT End of treatment; FU Follow-up; HRU Healthcare resource utilization; V Visit; W Week

Table 2 Study Assessments Schedule – Q8W regimen – YEAR 1[a]

Assessment/ activity	Refer to	Treatment							EOT[h]	IPD[i]	FU[h,i]	UNS[j]
		V1	V2	V3	V4	V5	V6	V7	4 wks after last dose	4 wks after last dose	12 wks after last dose	
		w0	W8	W16	W24	W32	W40	W48				
		Visit window (days)[c]										
		±0	±3	±3	±3	±3	±3	±3	+7	+7	±7	N/A
Informed consent	10.4	X										
Inclusion/exclusion criteria	3.1/3.2	X										
Medical, surgical, and asthma history	4.1.1	X[b]										
Hematology	5.2.1	X		X		X		X	X	X	X	
Serum chemistry	5.2.1	X						X	X	X	X	
Urine pregnancy test (dipstick)[d]	5.2.1.1	X	X	X	X	X	X	X	X	X	X	
FSH[e]	5.2.1.1	X										
Vital signs	5.2.2	X	X	X	X	X	X	X	X	X	X	X
ADA[f,g]	5.3.4	X		X		X		X	X	X	X	
Assessment of asthma exacerbations and asthma-related HRU	5.3.1/5.3.2	X	X	X	X	X	X	X	X	X	X	X
Adverse events	7.1	X[a]	X	X	X	X	X	X	X	X	X	X
Concomitant medication	3.5	X[a]	X	X	X	X	X	X	X	X	X	X
Administration of IP[i]	6.6	X	X	X	X	X	X	X				

[a] Visits and treatment to continue every 8 weeks until EOT. For Years 2, 3, and 4 (Week 56 [Visit 8] to Week 208 [Visit 27]), see Appendix G.
[b] Medical, surgical and asthma history, concomitant medications, and ongoing AEs must be entered manually. Data will not be integrated from BORA.
[c] All visits are to be scheduled from the date of enrolment, not from the date of previous visit
[d] For WOCBP, urine HCG test to be done at center on each treatment visit before IP administration.

[e] FSH test done only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 months to confirm postmenopausal status..

[f] ADA samples to be collected before IP administration.

[g] In case of anaphylaxis additional samples to be taken (see Section 6.7)

[h] EOT visit will occur when benralizumab has been approved and is available in the local market or the candidate drug is withdrawn from the approval process in the local market. For countries in which a marketing application is not submitted, patients will receive their last dose of benralizumab in December 2018, with EOT and FU visits in 1Q 2019.

[i] IPD visit to be conducted on early discontinuation of IP (see Section 3.6). Patients who complete an IPD visit will return 8 weeks (±7 days) later, ie, 12 weeks after the last dose of IP, for a final follow-up visit.

[j] Perform any assessments considered clinically relevant.

D Days; EOT End of treatment; FU Follow-up; HRU Healthcare resource utilization; V Visit; W Week

4.1 Enrolment period

4.1.1 Enrolment (Visit 1)

Each potential patient will provide written informed consent prior to any study specific procedures and undergo assessments applicable for the visit (see see Section 3.3, Table 1 or Table 2).

Visit 1 of this study will be scheduled to ensure uninterrupted dosing as patients transition from the predecessor study (BORA) into this safety extension study, regardless of their dosing regimen. In order to achieve this, patients must transition at the earliest possible odd-numbered BORA visit following all necessary approvals being in place at the study site, AND after database lock of the trial in which the patient entered this program (the latter will be confirmed to sites once this milestone reached). Patients may transition into this study only at Visits 5, 7, 9, or 11 of BORA.

Complete medical, surgical, and asthma history must be re-recorded in the eCRF for this study as data will not be integrated from BORA for the CSR. Ongoing AEs at the end of the predecessor study will be considered concurrent medical history and are to be re-entered manually into the eCRF for this study if considered clinically relevant by the Investigator. All concurrent medications taken by the patient at the time of entry into this study and the relevant condition for which treatment is being given are also to be re-entered manually into the eCRF for this study.

4.2 Treatment period

4.2.1 Dosing regimens

Patients previously randomized to the Q4W regimen of benralizumab in BORA will continue injections of active drug every 4 weeks in this open label study.

Patients previously randomized to the Q8W regimen in BORA will continue to receive active drug every 8 weeks in this open label study.

4.2.2 Treatment period assessments

Patients on the Q4W regimen will return to the study center every 4 weeks for treatment and any applicable study assessments. Patients on the Q8W regimen will return to the study center every 8 weeks for treatment and any applicable study assessments (see Table 1 and Table 2).

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

Patients will have scheduled visits at 4-week or 8-week intervals, depending on their assigned dosing regimen, to complete protocol-specific assessments and IP administration, as listed in Table 1 and Table 2. Restrictions as set out in Section 3.5.2 will continue to apply throughout the treatment period. In case of asthma worsening/exacerbation (see Section 5.3.1), patients

should be evaluated at the study center, when feasible and unscheduled (UNS) visit assessments (see Table 1 and Table 2) performed.

When benralizumab is approved and commercially available in the patient's local market or when the drug is removed from the approval process in the patient's local market, the patient will come to the center for the End of Treatment (EOT) visit. If transitioned to commercialized product at that time, no follow up visit is needed. If the patient will not be transitioned to commercialized product, the patient should come in for the FU visit and complete the study. For countries in which a marketing application is not submitted, patients will receive their last dose of benralizumab in December 2018, with EOT and FU visits in 1Q 2019.

Patients who prematurely discontinue IP (see Section 3.6) should return to the study center and complete procedures described for the IPD and Follow-up visits within 4 weeks (+7 days) and 12 weeks (±7 days) after the last dose of IP, respectively.

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

4.3 Follow-up period

Patients who complete an IPD visit and patients in countries in which a marketing application will not be submitted will return 8 weeks (±7 days) later, ie, 12 weeks after the last dose of IP, for a final follow-up visit.

5. STUDY ASSESSMENTS AND PROCEDURES

5.1 Efficacy assessments

There are no efficacy assessments in this study.

5.2 Safety assessments

All health-related assessments should be conducted as part of routine clinical care of the patient whether or not part of the protocol-specified assessments and must be documented in the patient's source documents. Only protocol-specified assessments will be captured in the eCRF.

5.2.1 Safety laboratory tests

Safety laboratory tests (list provided in 5.2.1) will be performed in a central laboratory. For information on methods of collection, assessment, labelling, storage and shipment of samples, please refer to the separate Laboratory Manual. Safety samples (as detailed in Table 3) will be collected in accordance with the schedules provided in Table 1 or Table 2.

Laboratory results should be reviewed by the Investigator/authorized delegate and evaluated for abnormalities. Any laboratory abnormalities considered significant in the Investigators'/authorized delegate's judgement should be reported as described to in Section 7.1.3.6.

A copy of the laboratory results report should be signed and dated by Investigator and retained at the study center. In contrast to the predecessor study, eosinophil, basophil, and monocyte results do not need to be redacted from the laboratory reports as this is an open-label study.

Serum chemistry		Hematology
Alkaline phosphatase	Gamma-GT (gamma-glutamyl transpeptidase)	Hematocrit
ALT (alanine aminotransferase)	Glucose	Hemoglobin
AST (aspartate aminotransferase)	Phosphorus	Mean corpuscular volume (MCV)
BUN (blood urea nitrogen)	Potassium	Platelet count
Calcium	Sodium	Red blood cell (RBC) count
Chloride	Total bilirubin	WBC count with differential
CO2 (carbon dioxide)	Total cholesterol	
Creatinine	Uric acid	

5.2.1.1 Pregnancy test

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

- FSH: To be done at Visit 1 in women <50 years who have been amenorrheic for >12 months to confirm postmenopausal status.
- Urine HCG: To be performed at the study center for all WOCBP (see Inclusion criterion 4, Section 3.1) at each treatment visit before IP administration using a dipstick. Positive urine test result must be confirmed with serum beta HCG. In the case of a positive serum beta HCG test result, the patient must be withdrawn from IP immediately.

5.2.2 Vital signs

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

The vital signs will be taken prior to IP administration and other study procedures at each study visit.

Body temperature will be measured in Celsius before IP administration in accordance with local standards.

5.3 Other assessments and procedures

5.3.1 Asthma exacerbations

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

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

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

5.3.2 Asthma-related hospitalizations and emergency department visits

Information on in-patient hospitalizations, number of days in the hospital, and emergency department (ED) visits will be collected by the Investigator/authorized delegate at each visit (as shown in Table 1 or Table 2) and recorded in the appropriate eCRF module.

Asthma-related hospitalization and ED visit information will be collected with a recall period of 'since the last scheduled visit'.

5.3.3 Pharmacodynamics

Blood eosinophil levels will be determined by CBC with differential at a central lab according to the schedule of assessments (see Table 1 and Table 2).

5.3.4 Immunogenicity

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

The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. Details of the analytical methods used will be described in a bioanalytical report.

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

5.3.5 Handling of biological samples

5.3.5.1 Labelling and shipment of biological samples

The Principal Investigator is to ensure that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials

containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

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

5.3.5.2 Chain of custody of biological samples

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

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

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

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

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

6. MANAGEMENT OF INVESTIGATIONAL PRODUCTS

6.1 Identity of investigational product(s)

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

Benralizumab administered in the study will be a clear to opalescent, colourless to yellow solution (Table 3).

Table 3 Identity of investigational product

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

6.2 Labelling

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

6.3 Storage

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

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

In the following cases:

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

the center staff should not use affected IP and should immediately contact an AstraZeneca representative for further guidance. Damaged IP should be documented via IWRS/IVRS (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. Certificates of delivery, destruction, and/or return should be signed.

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

6.5 Methods for assigning treatment groups

All patients will be assigned to the same dosing regimen in this safety extension study as they received in the predecessor study.

6.6 Investigational Product administration and treatment compliance

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

The IP will be administered at the study center on treatment visits and within visit windows as specified in Table 1 and Table 2. In cases when a treatment visit cannot be scheduled within the specified window, the IP administration should be skipped. If 2 consecutive doses of the IP are missed during course of the study the patient should be discontinued; please refer to Section 3.6.

Before investigational product administration

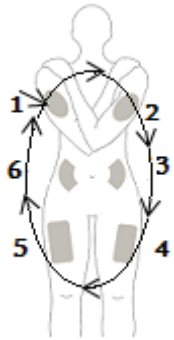
Prior to each IP administration:

- Investigator/authorized delegate will assess injection site as per standards of medical care
- For all WOCBP a urine pregnancy test will be done. IP must only be administered when the result of the test is negative (see Section 5.2.1.1)

IP administration

The IP will be administered by the Investigator/authorized delegate. It is advised that the site of injection of the IP be rotated such that the patient receives IP at a different anatomical site at each treatment visit. Suggested injection site rotation sequence is presented below (see Figure 1). The injection site must be recorded in the source documents and the eCRF at each treatment visit.

Figure 1 Injection sites and rotation scheme



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

After investigational product administration

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

Conditions requiring investigational product administration rescheduling

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

- The patient has an intercurrent illness, that in the opinion of the Investigator may compromise the safety of the patient in the study (eg, viral illnesses)
- The patient, in the opinion of the Investigator, is experiencing an acute or emerging asthma exacerbation
- The patient is febrile (≥38°C; ≥100.4°F) within 72 hours prior to the IP administration

6.7 Management of Investigational Product-related reactions

Appropriate drugs such as epinephrine, H1 and H2 antihistamines, and corticosteroids, as well as 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 E.

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:

- 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
- 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
- Reduced blood pressure after exposure

Patients should have pre-assessments (ie, vital signs) as part of routine clinical care prior to IP administration) and must be observed after IP administration for a minimum of 2 hours for the appearance of any acute drug reactions.

In order to help understand the potential drug-relatedness of any acute reaction, a blood sample should be drawn during any such 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

7.1 Adverse events

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

7.1.1 Definition of adverse events

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

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

7.1.2 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 fulfils one 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 one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol (CSP).

7.1.3 Recording of adverse events

7.1.3.1 Time period for collection of adverse events

All AEs, including SAEs, will be collected from the time the patient signs the informed consent at Visit 1 throughout the treatment period. Adverse events that are ongoing at the start of this study and are considered clinically relevant by the Investigator must be re-entered into the eCRF for this study as concurrent medical history.

7.1.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the last schedule visit in the study will be followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

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

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

7.1.3.3 Variables

The following variables will be collected for each AE;

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.1.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

7.1.3.4 Causality collection

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

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

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

7.1.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and

symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.1.3.6 Adverse events based on laboratory tests

The results from protocol-mandated laboratory tests will be summarized in the clinical study report. Deterioration as compared with baseline in protocol-mandated laboratory values 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 IP.

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

NB. Cases in which a patient shows an AST or ALT ≥3xULN or total bilirubin ≥ 2xULN may need to be reported as SAEs (please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions).

7.1.3.7 Symptoms of the disease under study

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

- The sign or symptom is serious according to definitions, see Section 7.1.2
- The patient discontinues the study due to the sign or symptom
- The sign or symptom is new to the patient or not consistent with the patient's pre-existing asthma history (defined as within 1 year of Visit 1) as judged by the investigator.

7.1.4 Reporting of serious adverse events

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

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

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1**

calendar day of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

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

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

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

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

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

7.2 Overdose

- An overdose with associated AEs will be recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module
- An overdose without associated symptoms will be reported on the Overdose CRF module only

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

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

For overdoses associated with a SAE, standard reporting timelines apply, see Section 7.1.4. For other overdoses, reporting should be done within 30 days.

7.3 Pregnancy

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

7.3.1 Maternal exposure

Fertile and sexually active patients or their partners should use effective contraceptive methods throughout the study and for at least 16 weeks (5 half-lives) after last administration of the IP.

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

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

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

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs (see Section 7.1.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

7.3.2 Paternal exposure

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

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

8. EVALUATION AND CALCULATION OF VARIABLES

8.1 Statistical considerations

- Analyses will be performed by AstraZeneca or its representatives
- The statistical analysis plan (SAP) will be prepared prior to first patient enrolled and any subsequent amendments will be documented,

8.2 Sample size estimate

Patients who have completed at least 16 weeks in Study D3250C00021 (BORA) after the requirement for approximately 1200 patients who will go on to complete BORA has been met

may be eligible to transition in to this study. This safety extension study will enroll approximately 700-1000 patients worldwide.

All analyses will be descriptive only. The study is not designed to power the statistical testing of any null hypothesis.

8.3 Definitions of analysis sets

8.3.1 Full analysis set

All patients who received at least 1 dose of IP will be included in the full analysis set. Patients will be classified according to the treatment to which they were assigned.

8.4 Variables for analyses

8.4.1 Safety variables

8.4.1.1 Calculation or derivation of safety variable(s)

The following safety data will be collected: hematology, clinical chemistry, and reported AEs. Change from study baseline (Visit 1) to each post-treatment time point will be calculated for relevant measurements.

Adverse events and SAEs will be reported and summarized by treatment group.

8.4.1.2 Analysis methods for safety variables

Adverse events will be summarized by treatment group. Adverse events will be listed for each patient and summarized by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by MedDRA, using n (%) and event rate per 100 patient years exposure. Laboratory safety variables will be summarized using standard summary statistics and plots as appropriate. Further details will be provided in the SAP.

8.4.2 Other assessments

8.4.2.1 Asthma exacerbations

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

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

Asthma exacerbations will be summarized descriptively.

8.4.2.2 Asthma-related Health Care Utilization

Asthma-related health care utilization by type of health care encounter will be summarized descriptively.

8.4.3 Immunogenicity variables

8.4.3.1 Calculation or derivation of immunogenicity variables

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

8.4.3.2 Analysis method for immunogenicity variables

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

8.5 Independent adjudication committee

An independent adjudication committee will be constituted to provide an independent, external, systematic and unbiased assessment of blinded data to confirm diagnosis of: 1) Investigator – reported non – fatal myocardial infarction, non – fatal stroke (hemorrhagic, ischemic, embolic), as well as cardiovascular deaths and 2) Investigator – reported malignancies during the Phase 3 trials. The committee will operate in accordance with an Adjudication Committee Charter/Manual of Operations, which will also provide detail on specific information the committee requires to enable a thorough adjudication.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study center personnel

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

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

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

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 case report forms (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 the electronic CRF (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 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 CSP 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 is to follow 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 Q2/Q3 2016.

Patients can remain in this study until benralizumab is available commercially in their local market or the candidate drug is withdrawn from the approval process. For countries in which a no application for commercialization of benralizumab is submitted, patients will receive their last dose of benralizumab in December 2018, with EOT and FU visits in 1Q 2019.

The study may be terminated at individual study centers if the study procedures are not being performed according to GCP. AstraZeneca may also terminate the entire study prematurely at its discretion, or 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 Center staff according to the Data Management Plan

AEs and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the terminology of the latest version of WHODrug Global B3 Format. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Center.

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

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

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable

regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The Informed Consent Forms will incorporate wording that complies with relevant data protection and privacy legislation (or, in some cases, these forms may be accompanied by a separate document incorporating this language, as applicable locally).

10.3 Ethics and regulatory review

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

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

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

AstraZeneca should approve any modifications to the Informed Consent Forms that are needed to meet local requirements.

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

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

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating 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 Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee 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 Ethics Committee see Section 10.3.

If a protocol amendment requires a change to a study center's Informed Consent Form, AstraZeneca and the study center's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

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

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the study center, including source data verification. The purpose

of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (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.

11. LIST OF REFERENCES

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

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

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

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

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

Friede and Schmidli 2010
Friede, T., Schmidli, H.. Blinded sample size reestimation with negative binomial counts in superiority and non-inferiority trials. Methods of Information in Medicine. 2010 Jan, 49, 6, 618-24

GINA 2015
Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) April 2015. Available from: URL: http://www.ginasthma.org/guidelines-ginareport-global-strategy-for-asthma.html.

Green et al 2002
Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomized controlled trial. Lancet. 2002 Nov 30;360(9347):1715–21.

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

Hochberg 1988
Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988;75:800-2.

Holm 1979
Holm S. A simple sequentially rejective multiple test procedure. Scand.J. Statist.1979;6:65-70.

Jayaram et al 2006
Jayaram L, Pizzichini MM, Cook RJ, Boulet LP, Lemière C, Pizzichini E, et al. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. Eur Respir J. 2006 Mar;27(3):483-94.

Juniper et al 1994
Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life instrument. J Clin Epidemiol. 1994; 47: 81-87.

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

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

Kerstjens et al 2012
Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med. 2012 Sep 27;367(13):1198-207.

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

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

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

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

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

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

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

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

Pavord et al 2012
Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM):a multicentre, double-blind, placebo-controlled trial. Lancet. 2012,Aug;380:651-59.

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

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

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

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

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

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

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

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Clinical Study Protocol Appendix B

Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00037
Edition Number	1.0
Date	11 January 2016

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

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Clinical Study Protocol Appendix C	
Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00037
Edition Number	1.0
Date	11 January 2016

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

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Clinical Study Protocol Appendix D

Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00037
Edition Number	1.0
Date	11 January 2016

Appendix D
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

TABLE OF CONTENTS PAGE

1. INTRODUCTION

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

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

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

2. DEFINITIONS

Potential Hy's Law (PHL)

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

Hy's Law (HL)

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

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

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

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

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

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

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

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

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

If Yes:

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

- If there is no significant change no action is required

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

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

8. REFERENCES

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

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Clinical Study Protocol Appendix E

Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00037
Edition Number	1.0
Date	11 January 2016

Appendix E
Anaphylaxis: signs and symptoms, management

1. INTRODUCTION

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

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

2. CLINICAL CRITERIA FOR DEFINING ANAPHYLAXIS AND IMMUNE COMPLEX DISEASE

Anaphylaxis

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

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

   AND AT LEAST ONE OF THE FOLLOWING

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

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

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

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

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

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

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

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

Immune Complex Disease

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

3. SIGNS AND SYMPTOMS AND MANAGEMENT OF ACUTE ANAPHYLAXIS

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

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

Other earlier or concomitant signs and symptoms can include:

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

- Lightheadedness
- Headache
- Uterine cramps
- Generalized warmth

4. MANAGEMENT OF ACUTE ANAPHYLAXIS

4.1 Immediate intervention

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

4.2 Possibly appropriate, subsequent measures depending on response to epinephrine

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

(b) Establish and maintain airway.

(c) Administer oxygen.

(d) Establish venous access.

(e) Normal saline IV for fluid replacement.

4.3 Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion.

(b) Consider H1 and H2 antihistamines.

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

(d) Consider systemic corticosteroids.

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

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

(g) Consider atropine for symptomatic bradycardia.

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

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

Adapted from Kemp et al 2008.

5. REFERENCES

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

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

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Clinical Study Protocol Appendix F	
Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00037
Edition Number	2.0
Date	18 July 2017

Appendix F
Restricted and prohibited medications

PROHIBITED AND RESTRICTED MEDICATIONS

Other medication restrictions

Table1 Other medication restrictions

Medication	Prohibited/restricted	Details
Live Attenuated Vaccines	Prohibited	Not allowed 30 days prior to randomization; during treatment period, and 16 weeks (5 half-lives) after the last dose
Inactive/killed vaccinations (e.g. inactive influenza)	Restricted	Allowed provided they are not administered within 1 week before/after any IP administration
Any immunomodulators or immunosuppressives except systemic steroids used: 1) for the treatment of asthma exacerbations and 2) as intraarticular injections	Prohibited	Not allowed within 3 months prior to the date informed consent is obtained; during treatment period; 3 months or 5 half -lives (whichever is longer) after last dose
Blood products or immunoglobulin therapy	Prohibited	Not allowed 30 days prior to date of ICF; during treatment period
Any marketed (e.g. omalizumab) or investigational biologic treatment	Prohibited	Not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1; during treatment period; 4 months or 5 half-lives (whichever is longer) after the last dose of the investigational product

Medication	Prohibited/restricted	Details
Other investigational Products (including investigational use of an approved drug)	Prohibited	Not allowed 30 Days or 5 half-lives (whichever is longer) prior to Visit 1; during treatment period
Allergen Immunotherapy	Restricted	Allowed if on stable therapy, or stable seasonal therapy, for at least 30 days prior to date of ICF; no anticipated change during treatment period; immunotherapy injections must be separated from IP injections by at least 7 calendar days
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases	Prohibited	Not allowed 30 days prior to Visit 1; during the treatment period
Non-selective oral β-adrenergic antagonist (e.g. propranolol)	Prohibited	Patients currently using any non-selective oral β-adrenergic antagonist at the time of enrolment are not eligible for the study. Not allowed during treatment period.

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Clinical Study Protocol Appendix G	
Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00037
Edition Number	2.0
Date	18 July 2017

Appendix G
Study Plan and Procedures – Years 2, 3, and 4

STUDY PLAN AND PROCEDURES

Q4W REGIMEN – YEAR 2

Table 1 Study Assessments Schedule – Q4W regimen – Year 2

Assessment/ activity	Refer to	Treatment													EOT[e]	IPD[f]	FU[e,f]	UNS[g]
		V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27				
		w56	w60	w64	w68	w72	w76	w80	w84	w88	w92	w96	w100	w104	4 wks after last dose	4 wks after last dose	12 wks after last dose	
		Visit window (days) [a]																
		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	±7	N/A
Hematology	5.2.1					X						X			X	X	X	
Serum chemistry	5.2.1											X			X	X	X	
Urine pregnancy test (dipstick) [b]	5.2.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	5.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
ADA [c,d]	5.3.4					X						X			X	X	X	
Assessment of asthma exacerbations and asthma-related HRU	5.3.1/5.3.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	7.1	X	X	X	X	X	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	X	X	X	X	X
Administration of IP[f]	6.6	X	X	X	X	X	X	X	X	X	X	X	X	X				

[a] All visits are to be scheduled from the date of enrolment, not from the date of previous visit
[b] For WOCBP, urine HCG test to be done at center on each treatment visit before IP administration.
[c] ADA samples to be collected before IP administration.
[d] In case of anaphylaxis additional samples to be taken (see Section 6.7)

[e] EOT visit will occur when benralizumab has been approved and is available in the local market or the candidate drug is withdrawn from the approval process in the local market. For countries in which a marketing application is not submitted, patients will receive their last dose of benralizumab in December 2018 with EOT and FU visits in 1Q 2019.

[f] IPD visit to be conducted on early discontinuation of IP (see Section 3.6). Patients who complete an IPD visit will return 8 weeks (±7 days) later, ie, 12 weeks after the last dose of IP, for a final follow-up visit.

[g] Perform any assessments considered clinically relevant.

D Days; EOT End of treatment; FU Follow-up; HRU Healthcare resource utilization; V Visit; W Week

Q4W REGIMEN – YEAR 3

Table 2 Study Assessments Schedule – Q4W regimen – Year 3

Assessment/ activity	Refer to	Treatment													EOT[e]	IPD[f]	FU[e,f]	UNS[g]
		V28	V29	V30	V31	V32	V33	V34	V35	V36	V37	V38	V39	V40				
		w108	w112	w116	w120	w124	w128	w132	w136	w140	w144	w148	w152	w156	4 wks after last dose	4 wks after last dose	12 wks after last dose	
		Visit window (days) [a]																
		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	±7	N/A
Hematology	5.2.1				X						X				X	X	X	
Serum chemistry[j]	5.2.1										X				X	X	X	
Urine pregnancy test (dipstick) [b]	5.2.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	5.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
ADA [c,d]	5.3.4				X						X				X	X	X	
Assessment of asthma exacerbations and asthma-related HRU	5.3.1/5.3.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	7.1	X	X	X	X	X	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	X	X	X	X	X
Administration of IP[f]	6.6	X	X	X	X	X	X	X	X	X	X	X	X	X				

[a] All visits are to be scheduled from the date of enrolment, not from the date of previous visit
[b] For WOCBP, urine HCG test to be done at center on each treatment visit before IP administration.
[c] ADA samples to be collected before IP administration.
[d] In case of anaphylaxis additional samples to be taken (see Section 6.7)

[e] EOT visit will occur when benralizumab has been approved and is available in the local market or the candidate drug is withdrawn from the approval process in the local market. For countries in which a marketing application is not submitted, patients will receive their last dose of benralizumab in December 2018 with EOT and FU visits in 1Q 2019.

[f] IPD visit to be conducted on early discontinuation of IP (see Section 3.6). Patients who complete an IPD visit will return 8 weeks (±7 days) later, ie, 12 weeks after the last dose of IP, for a final follow-up visit.

[g] Perform any assessments considered clinically relevant.

D Days; EOT End of treatment; FU Follow-up; HRU Healthcare resource utilization; V Visit; W Week

Q4W REGIMEN – YEAR 4

Table 3 Study Assessments Schedule – Q4W regimen – Year 4

Assessment/ activity	Refer to	Treatment													**EOT[e]**	**IPD[f]**	**FU[e,f]**	**UNS[g]**
		V41	V42	V43	V44	V45	V46	V47	V48	V49	V50	V51	V52	V53				
		w160	w164	w168	w172	w176	w180	w184	w188	w192	w196	w200	w204	w208	4 wks after last dose	4 wks after last dose	12 wks after last dose	
		Visit window (days) [a]																
		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	±7	N/A
Hematology	5.2.1			**X**						**X**					**X**	**X**	**X**	
Serum chemistry	5.2.1									**X**					**X**	**X**	**X**	
Urine pregnancy test (dipstick) [b]	5.2.1.1	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Vital signs	5.2.2	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**
ADA [c,d]	5.3.4			**X**						**X**					**X**	**X**	**X**	
Assessment of asthma exacerbations and asthma-related HRU	5.3.1/5.3.2	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse events	7.1	**X**	**X**	**X**	**X**	**X**	**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**	**X**	**X**	**X**	**X**	**X**
Administration of IP[f]	6.6	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**				

[a] All visits are to be scheduled from the date of enrolment, not from the date of previous visit
[b] For WOCBP, urine HCG test to be done at center on each treatment visit before IP administration.
[c] ADA samples to be collected before IP administration.
[d] In case of anaphylaxis additional samples to be taken (see Section 6.7)

[e] EOT visit will occur when benralizumab has been approved and is available in the local market or the candidate drug is withdrawn from the approval process in the local market. For countries in which a marketing application is not submitted, patients will receive their last dose of benralizumab in December 2018 with EOT and FU visits in 1Q 2019.

[f] IPD visit to be conducted on early discontinuation of IP (see Section 3.6). Patients who complete an IPD visit will return 8 weeks (±7 days) later, ie, 12 weeks after the last dose of IP, for a final follow-up visit.

[g] Perform any assessments considered clinically relevant.

D Days; EOT End of treatment; FU Follow-up; HRU Healthcare resource utilization; V Visit; W Week

Q8W REGIMEN – YEAR 2

Table 4 Study Assessments Schedule – Q8W regimen – YEAR 2

Assessment/ activity	Refer to	Treatment							EOT[e]	IPD[f]	FU[e,f]	UNS[g]
		V8	V9	V10	V11	V12	V13	V14	4 wks after last dose	4 wks after last dose	12 wks after last dose	
		W56	W64	W72	W80	W88	W96	W104				
		Visit window (days) [b]										
		±3	±3	±3	±3	±3	±3	±3	+7	+7	±7	N/A
Hematology	5.2.1			X			X		X	X	X	
Serum chemistry	5.2.1						X		X	X	X	
Urine pregnancy test (dipstick) [a]	5.2.1.1	X	X	X	X	X	X	X	X	X	X	
Vital signs	5.2.2	X	X	X	X	X	X	X	X	X	X	X
ADA[c,d]	5.3.4			X			X		X	X	X	
Assessment of asthma exacerbations and asthma-related HRU	5.3.1/5.3.2	X	X	X	X	X	X	X	X	X	X	X
Adverse events	7.1	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
Administration of IP [f]	6.6	X	X	X	X	X	X	X				

[a] All visits are to be scheduled from the date of enrolment, not from the date of previous visit
[b] For WOCBP, urine HCG test to be done at center on each treatment visit before IP administration.
[c] ADA samples to be collected before IP administration.
[d] In case of anaphylaxis additional samples to be taken (see Section 6.7)
[e] EOT visit will occur when benralizumab has been approved and is available in the local market or the candidate drug is withdrawn from the approval process in the local market. For countries in which a marketing application is not submitted, patients will receive their last dose of benralizumab in December 2018 with EOT and FU visits in 1Q 2019.
[f] IPD visit to be conducted on early discontinuation of IP (see Section 3.6). Patients who complete an IPD visit will return 8 weeks (±7 days) later, ie, 12 weeks after the last dose of IP, for a final follow-up visit.
[g] Perform any assessments considered clinically relevant.

D Days; EOT End of treatment; FU Follow-up; HRU Healthcare resource utilization; V Visit; W Week

Q8W REGIMEN – YEAR 3

Table 5 Study Assessments Schedule – Q8W regimen – YEAR 3

Assessment/ activity	Refer to	Treatment						EOT[e]	IPD[f]	FU[e,f]	UNS[g]
		V15	V16	V17	V18	V19	V20	4 wks after last dose	4 wks after last dose	12 wks after last dose	
		W112	W120	W128	W136	W144	W152				
		Visit window (days) [a]									
		±3	±3	±3	±3	±3	±3	+7	+7	±7	N/A
Hematology	5.2.1		X			X		X	X	X	
Serum chemistry	5.2.1					X		X	X	X	
Urine pregnancy test (dipstick) [b]	5.2.1.1	X	X	X	X	X	X	X	X	X	
Vital signs	5.2.2	X	X	X	X	X	X	X	X	X	X
ADA[c,d]	5.3.4		X			X		X	X	X	
Assessment of asthma exacerbations and asthma-related HRU	5.3.1/5.3.2	X	X	X	X	X	X	X	X	X	X
Adverse events	7.1	X	X	X	X	X	X	X	X	X	X
Concomitant medication	3.5	X	X	X	X	X	X	X	X	X	X
Administration of IP [f]	6.6	X	X	X	X	X	X				

[a] All visits are to be scheduled from the date of enrolment, not from the date of previous visit
[b] For WOCBP, urine HCG test to be done at center on each treatment visit before IP administration.
[c] ADA samples to be collected before IP administration.
[d] In case of anaphylaxis additional samples to be taken (see Section 6.7)
[e] EOT visit will occur when benralizumab has been approved and is available in the local market or the candidate drug is withdrawn from the approval process in the local market. For countries in which a marketing application is not submitted, patients will receive their last dose of benralizumab in December 2018 with EOT and FU visits in 1Q 2019.
[f] IPD visit to be conducted on early discontinuation of IP (see Section 3.6). Patients who complete an IPD visit will return 8 weeks (±7 days) later, ie, 12 weeks after the last dose of IP, for a final follow-up visit.
[g] Perform any assessments considered clinically relevant.

D Days; EOT End of treatment; FU Follow-up; HRU Healthcare resource utilization; V Visit; W Week

Q8W REGIMEN – YEAR 4

Table 6 Study Assessments Schedule – Q8W regimen – YEAR 4

Assessment/ activity	Refer to	Treatment							EOT[e]	IPD[f]	FU[e,f]	UNS[g]
		V21	V22	V23	V24	V25	V26	V27	4 wks after last dose	4 wks after last dose	12 wks after last dose	
		W160	W168	W176	W184	W192	W200	W208				
		Visit window (days) [a]										
		±3	±3	±3	±3	±3	±3	±3	+7	+7	±7	N/A
Hematology	5.2.1		X			X			X	X	X	
Serum chemistry	5.2.1					X			X	X	X	
Urine pregnancy test (dipstick) [b]	5.2.1.1	X	X	X	X	X	X	X	X	X	X	
Vital signs	5.2.2	X	X	X	X	X	X	X	X	X	X	X
ADA[c,d]	5.3.4		X			X			X	X	X	
Assessment of asthma exacerbations and asthma-related HRU	5.3.1/5.3.2	X	X	X	X	X	X	X	X	X	X	X
Adverse events	7.1	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
Administration of IP [f]	6.6	X	X	X	X	X	X	X				

[a] All visits are to be scheduled from the date of enrolment, not from the date of previous visit
[b] For WOCBP, urine HCG test to be done at center on each treatment visit before IP administration.
[c] ADA samples to be collected before IP administration.
[d] In case of anaphylaxis additional samples to be taken (see Section 6.7)
[e] EOT visit will occur when benralizumab has been approved and is available in the local market or the candidate drug is withdrawn from the approval process in the local market. For countries in which a marketing application is not submitted, patients will receive their last dose of benralizumab in December 2018 with EOT and FU visits in 1Q 2019.
[f] IPD visit to be conducted on early discontinuation of IP (see Section 3.6). Patients who complete an IPD visit will return 8 weeks (±7 days) later, ie, 12 weeks after the last dose of IP, for a final follow-up visit.
[g] Perform any assessments considered clinically relevant.

D Days; EOT End of treatment; FU Follow-up; HRU Healthcare resource utilization; V Visit; W Week