AstraZeneca

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A Multicenter, Double-blind, Randomized, Parallel Group, Phase 3 Safety Extension Study to Evaluate the Safety and Tolerability of Benralizumab (MEDI-563) in Asthmatic Adults and Adolescents on Inhaled Corticosteroid Plus Long-acting β2 Agonist (BORA)

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Redacted

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

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1	01 September 2015		
2	13 January 2016		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change
1	09 September 2016		

PROTOCOL SYNOPSIS

A Multicenter, Double-blind, Randomized, Parallel Group, Phase 3 Safety Extension Study to Evaluate the Safety and Tolerability of Benralizumab (MEDI-563) in Asthmatic Adults and Adolescents on Inhaled Corticosteroid Plus Long-acting β2 Agonist (BORA)

International Co-ordinating Investigator

Study center(s) and number of patients planned

This study will be conducted worldwide in 448 centers. Patients who complete Study D3250C00017, D3250C00018, or D3250C00020 on investigational product may be eligible for this study. With an estimated rollover rate of >90% from these preceding studies this safety extension study enrolled 2133 patients worldwide.

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2014	Phase 3
Estimated date of last patient completed	Q3 2018	

Objectives

(a) Primary Objective

Objective	Endpoint
1. To assess the safety and tolerability of 2 dosing regimens of benralizumab for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To assess the safety and tolerability of 2 dosing regimens of benralizumab for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• Number of AEs/SAEs • Laboratory variables • Physical examination

(b) Secondary Objectives

Objective	Endpoint
1. To evaluate the effect of 2 dosing regimens of benralizumab on asthma exacerbations in adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To evaluate the effect of 2 dosing regimens of benralizumab on asthma exacerbations in adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• Annual asthma exacerbation rate, where an asthma exacerbation is defined by a worsening of asthma requiring the use of systemic corticosteroids for at least 3 days, and/or an in-patient hospitalization, and/or an emergency department or urgent care visit.
1. To evaluate the effect of 2 dosing regimens of benralizumab on health care utilization and work and productivity loss for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To evaluate the effect of 2 dosing regimens of benralizumab on health care utilization and work and productivity loss for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• WPAI+CIQ • Hospitalizations, ED visits, urgent care visits and all other outpatient visits due to asthma

Objective	Endpoint
1. To assess the effect of 2 dosing regimens of benralizumab on asthma related and general health-related quality of life for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To assess the effect of 2 dosing regimens of benralizumab on asthma related and general health-related quality of life for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• AQLQ(S)+12 • EQ-5D-5L
1. To assess the effect 2 dosing regimens of benralizumab on asthma control for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To assess the effect 2 dosing regimens of benralizumab on asthma control for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• ACQ-6
1. To evaluate the pharmacokinetics and immunogenicity of 2 dosing regimens of benralizumab for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To evaluate the pharmacokinetics and immunogenicity of 2 dosing regimens of benralizumab for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• PK parameters • Anti-drug antibodies (ADA)
1. To assess the effect of 2 dosing regimens of benralizumab on pulmonary function for adult patients during the 56-week treatment period (16 weeks from day of last dose) 2. To assess the effect of 2 dosing regimens of benralizumab on pulmonary function for adolescent patients during the 108-week treatment period (16 weeks from day of last dose)	• Pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at the study center

Objective	Endpoint
1. To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels for adult patients during the 56-week treatment period and through follow-up period (16 weeks from day of last dose) 2. To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• Blood eosinophils

Study design

This is a double-blind, randomized, parallel group, extension study designed to evaluate the safety and tolerability of a fixed 30 mg dose of benralizumab administered subcutaneously (SC). Patients who complete 1 of the predecessor studies D3250C00017, D3250C00018, or D3250C00020 on investigational product may be eligible to enrol into this study.

After a minimum of 1200 patients have been enrolled in this study, subsequent patients (up to a maximum of 2200 total for the study), who complete a minimum of 16 weeks, and no more than 40 weeks, in this study, will be given the option to transition to an open-label safety extension study, Study D3250C00037 (MELTEMI), which retains patients on the same treatment regimen as in this study and contains a simplified set of study assessments.

Patients choosing to enter Study D3250C00037 will complete an end-of-treatment (EOT) visit in this study before transitioning. Adolescent patients, patients from Japan and South Korea, and any patient who chooses not to enter Study D3250C00037 will remain in this study through IPD or EOT and FU.

Once the blind is broken in the predecessor studies, this study (BORA) becomes a single-blind design for those patients who had been on active treatment in the predecessor studies. The study will become single-blind for all remaining patients at the time of the Japanese EOT analysis. While the Sponsor will be unblinded to regimen for analysis purposes, study conduct and blinding at the site and patient level will remain unchanged.

<u>Adults</u>

Patients previously assigned to an active treatment arm in the predecessor study

Patients previously randomized to the every 4 weeks (Q4W) regimen of benralizumab will continue injections of active drug every 4 weeks.

Patients previously randomized to the every 8 week (Q8W) regimen will continue to receive active drug every 8 weeks with placebo (dummy) injections administered at the 4-week interim treatment visits in order to maintain the blind.

Patients previously assigned to the placebo arm in the predecessor study

All adult patients previously assigned to the placebo arm in the predecessor study will be re-randomized to either the Q4W or Q8W regimen (first 3 doses administered every 4 weeks followed by every 8 weeks thereafter). Patients on the Q4W regimen will receive active drug every 4 weeks. Patients on the Q8W regimen will receive active drug at Visit 1 (Week 0), Visit 2 (Week 4), Visit 3 (Week 8), followed by alternating monthly SC injections of placebo and active drug, eg, placebo at Visit 4 (Week 12), active drug at Visit 5 (Week 16), placebo at Visit 6 (Week 20), and so on in order to maintain the blind relative to the Q4W regimen.

Adolescents outside the European Union[1]

Adolescents previously assigned to an active treatment arm in the predecessor study

Adolescents previously randomized to the Q4W regimen of benralizumab will continue injections of active drug every 4 weeks. Patients previously randomized to the Q8W regimen will continue to receive active drug every 8 weeks with placebo (dummy) injections administered at the 4-week interim treatment visits in order to maintain the blind.

Adolescents previously assigned to the placebo arm in the predecessor study

Adolescents previously assigned to the placebo arm in the predecessor study will be re-randomized to either the Q4W or Q8W regimen (first 3 doses administered every 4 weeks followed by every 8 weeks thereafter). Patients on the Q4W regimen will receive active drug every 4 weeks. Patients on the Q8W regimen will receive active drug at Visit 1 (Week 0), Visit 2 (Week 4), Visit 3 (Week 8), followed by alternating monthly SC injections of placebo and active drug, eg, placebo at Visit 4 (Week 12), active drug at Visit 5 (Week 16), placebo at Visit 6 (Week 20), and so on in order to maintain the blind relative to the Q4W regimen.

Adolescents within the European Union

Adolescents previously assigned to an active treatment arm in the predecessor study

Adolescents within the European Union (EU) will continue to receive only the Q8W dosing regimen as per the predecessor study. In order to maintain the blind of the predecessor study, this group will receive injections every 4 weeks for the first 3 doses (active drug at Visits 1 and 3, placebo administered at Visit 2) followed by every 8 weeks thereafter.

Adolescents previously assigned to the placebo arm in the predecessor study

[1] For the purposes of this study the European Union (EU) is defined as consisting of the following countries: Bulgaria, Czech Republic, France, Germany, Italy, Poland, Romania, Spain, Sweden and the United Kingdom.

Adolescents within the EU who were randomized to placebo in the predecessor study will be assigned to benralizumab 30 mg Q8W in this study (every 4 weeks for the first 3 doses followed by every 8 weeks thereafter).

After the first 3 doses, adolescent patients within the EU will be receiving open-label treatment with IP administered at their bimonthly visit; however, they will still follow an every 4 weeks study visit schedule (see Table of Assessments, Table 2).

Target patient population

Patients who complete Study D3250C00017, D3250C00018, or D3250C00020 on investigational product may be eligible for this study.

Investigational product and mode of administration

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

Dosage

Refer to Study Design section above.

Duration of treatment

Adults: This is a 68-week study with the last dose of study drug administered at Week 52. An end of treatment (EOT) visit will be conducted at Week 56. A final follow-up visit will be conducted at Week 68, which is 16 weeks after the last dose of study drug.

The total planned study duration is 68 weeks.

Adolescents: This is a 120-week study with the last dose of study drug administered at Week 104. An EOT visit will be conducted at Week 108. A final follow-up visit will be conducted at Week 120, which is 16 weeks after the last dose of study drug.

The total planned study duration is 120 weeks.

Statistical methods

All safety and efficacy parameters will be analyzed descriptively based on the full analysis set. The full analysis set includes all randomized patients who received any dose of IP.

Patients that enter the predecessor study as an adolescent (at Visit 1 of the predecessor study) will continue to be considered as an adolescent throughout this study, and will thus be assigned to treatment regimen and assessments of an adolescent, irrespective of when they reach 18 years of age.

Data from adult patients choosing to enter the safety extension study, D3250C00037, will be summarized separately from those remaining in this study.

The adult completion analysis of BORA will be conducted when all adult patients have completed the study, and all adolescent patients have completed the first 56 weeks of treatment within BORA. A subsequent analysis in adolescent patients will be completed when all adolescent patients have completed the study.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APFS	Accessorized pre-filled syringe
AQLQ(S)+12	Standardised Asthma Quality of Life Questionnaire for 12 Years and Older
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
Beta-hCG	Beta- human chorionic gonadotropin
BP	Blood pressure
BUN	Blood urea nitrogen
Cmax	Maximum drug concentration
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency department
EC90	Benralizumab serum concentration corresponding to 90% of maximum efficacy
ED90	Benralizumab dose corresponding to 90% of maximum efficacy
EOT	End of treatment
EU	European Union

Abbreviation or special term	Explanation
EXACA	Exacerbation eCRF
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
Gamma-GT	Gamma-glutamyl transpeptidase
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
GLI	The Global Lung Function Initiative
HCP	Health care provider
HCU	Healthcare Utilization
HDL cholesterol	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
Ig	Immunoglobulin
IL	Interleukin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-5Rα	Interleukin-5 receptor alpha subunit
IM	Intramuscular
ICI	International Coordinating Investigator
IP	Investigational product
IPD	Premature Investigational Product Discontinuation
IRB	Institutional Review Board
ISF	Investigator Study File
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-acting β_2 agonists

Abbreviation or special term	Explanation
LAMA	Long-acting anti-muscarinic
LDH	Lactate dehydrogenase
LDL cholesterol	Low density lipoprotein cholesterol
LFT	Liver function test
LTRA	Leukotriene receptor antagonists
MED	Medication
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
nAb	Neutralizing antibodies
NAEPP	National Asthma Education Prevention Program
OAE	Other significant adverse event
OCS	Oral corticosteroids
PEF	Peak expiratory flow
PFS	Pre-filled syringe
PK	Pharmacokinetic(s)
PN	Predicted normal
Post-BD	Post-bronchodilator
Pre-BD	Pre-bronchodilator
PRO	Patient-reported outcome
ROW	Rest of World (countries outside European Union)
RBC	Red blood cell
SABA	Short-acting β_2 agonists
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
TBNK	T cell, B cell and Natural Killer cell
TEAE	Treatment Emergent Adverse Event
TH2	T helper 2
TLC	Total lung capacity
ULN	Upper limit of normal

Abbreviation or special term	Explanation
UNS	Unscheduled
US	United States of America
WBC	White blood cell
WBDC	Web-based Data Capture
WOCBP	Women of childbearing potential
WPAI+CIQ	Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions

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. Symptom control in children and adolescents with asthma can be similarly challenging, due in part to the limitations of current therapeutic modalities. Longer treatment courses, over a period of months or years, and higher medication doses may be required to achieve the maximum possible improvement in lung function in children older than 5 years (GINA 2015). Therefore, there remains an unmet medical need for patients whose asthma is not controlled by existing therapies.

The observed variability in clinical response to currently available asthma therapies appears to be related, in part, to distinctive inflammatory phenotypes (Wenzel 2012). In particular, asthma associated with eosinophilic inflammation in the airway (often referred to as eosinophilic asthma) is common (approximately 40% to 60% of asthmatics) with the degree of eosinophilia associated with clinical severity including the risk of asthma exacerbations (Bousquet et al 1990; Louis et al 2000; Di Franco et al 2003; Scott and Wardlaw 2006, Simpson et al 2006; Zhang and Wenzel 2007). 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 extremely limited.

In previous clinical studies, benralizumab administration resulted in rapid and prolonged depletion of eosinophils in the peripheral blood and 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 in asthma patients who have completed 1 of the 3 predecessor studies: D3250C00017, D3250C00018, or D3250C00020.

1.3 Rationale for study design, doses, and control groups

This is a global study designed to continue to investigate the safety of benralizumab in severe asthma patients on ICS-LABA therapy with or without chronic oral corticosteroids (OCS) and/or other asthma controllers. All patients who were assigned to the placebo regimen during the predecessor study will be reassigned to receive active drug, while those who received active drug during the predecessor study will continue on that same regimen. This will allow for the collection of safety and efficacy information in some patients for up to 2 continuous years in adults and 3 continuous years in adolescents.

Once the blind is broken in the predecessor studies, this study (BORA) becomes a single-blind design for those patients who had been on active treatment in the predecessor studies. The study will become single blind for all remaining patients at the time of the Japanese EOT analysis (see Section 8.5.4). While the Sponsor will be unblinded to regimen for analysis purposes, study conduct and blinding at the site and patient level will remain unchanged.

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.

The efficacy and safety of benralizumab in asthmatic patients is being evaluated in studies D3250C00017, D3250C00018, and D3250C00020. In this study, additional risk/benefit information will be generated with regard to the impact of benralizumab on asthma exacerbations, lung function, asthma control metrics, AEs and SAEs, and laboratory data. Additional information with regard to peripheral blood eosinophil levels and benefit/risk will be collected.

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

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

1.5 Overall study design

This is a double-blind, randomized, parallel group, study designed to evaluate the safety and tolerability of a fixed 30 mg dose of benralizumab administered subcutaneously (SC).

Eligible patients will transition from the predecessor study into this follow-on study at the End-of-Treatment (EOT) visit of the predecessor study. Visit 1 of this extension study will be scheduled on the same day as the EOT visit of the predecessor study (see Section 4.1.1). Duplicate assessments will not be required.

Patients will be maintained on their currently prescribed ICS-LABA therapy(ies), throughout the treatment period, unless any changes are considered necessary/appropriate at the discretion of the Investigator.

In this study, patients will receive 56 weeks of study treatment (108 weeks for adolescents). Patients who enter the predecessor study as an adolescent (at Visit 1 of the predecessor study) will continue to be considered an adolescent throughout this study, and will thus be assigned

to the treatment regimen and assessments of an adolescent, irrespective of when they reach 18 years of age.

A follow-up visit will be conducted at Week 68 (Week 120 for adolescents), which is 16 weeks after the last dose of study drug.

The total patient population for this study will be approximately 2200 patients, comprising patients from Studies D3250C00017, D3250C00018, and D3250C00020. Approximately 1200 adult patients will remain in this study through IPD or EOT and FU. The remaining approximately 700-1000 adult patients will stay in BORA for at least 16 weeks and not more than 40 weeks, and will then be asked to transition to an open-label safety extension study, Study D3250C00037 (MELTEMI). Investigators will be provided with the list of patients who will be asked to participate in Study D3250C00037.

A minimum of 1200 patients is considered sufficient to address the primary objective of safety and tolerability in the on-treatment and 16-week safety follow-up period of this study. The safety extension study, MELTEMI, will allow remaining patients to continue to receive benralizumab until it is available in their local market, until it has been withdrawn from the approval process in their local market, or until the end of December 2018 in those countries in which a marketing application will not be submitted. The minimum 16-week treatment period prior to transition to MELTEMI ensures that any patients previously randomized to placebo have completed monthly study visits and assessments for the first 3 active doses within this study before transitioning to MELTEMI.

Patients will begin to transition from BORA into this study only after the database lock of the initial study into which the individual patient was recruited has been reached, and a positive risk/benefit evaluation of the results from CALIMA & SIROCCO has taken place. In order to maintain the blind of ZONDA, transition of patients that originate from that study will commence only after the database lock of ZONDA. To ensure this strategy is followed, study sites will be instructed by the Sponsor at which point transition of individual patients may begin.

To meet certain health authority obligations, adolescent patients and patients from Japan and South Korea will remain in this study through IPD or EOT and FU. Patients choosing not to transition into MELTEMI will be allowed to remain in this study through IPD or EOT and FU.

Adults

Patients previously assigned to an active treatment arm in the predecessor study

Patients previously randomized to the every 4 weeks (Q4W) regimen of benralizumab will continue injections of active drug every 4 weeks.

Patients previously randomized to the every 8 week (Q8W) regimen will continue to receive active drug every 8 weeks with placebo (dummy) injections administered at the 4-week interim treatment visits in order to maintain the blind.

Patients previously assigned to the placebo arm in the predecessor study

All adult patients previously assigned to the placebo arm in the predecessor study will be re-randomized to either the Q4W or Q8W regimen (first 3 doses administered every 4 weeks followed by every 8 weeks thereafter). Patients on the Q4W regimen will receive active drug every 4 weeks. Patients on the Q8W regimen will receive active drug at Visit 1 (Week 0), Visit 2 (Week 4), Visit 3 (Week 8), followed by alternating monthly SC injections of placebo and active drug, eg, placebo at Visit 4 (Week 12), active drug at Visit 5 (Week 16), placebo at Visit 6 (Week 20), and so on in order to maintain the blind relative to the Q4W regimen.

Adolescents outside the European Union (EU)[2]

Adolescents previously assigned to an active treatment arm in the predecessor study

Adolescents previously randomized to the Q4W regimen of benralizumab will continue injections of active drug every 4 weeks.

Patients previously randomized to the Q8W regimen will continue to receive active drug every 8 weeks with placebo (dummy) injections administered at the 4-week interim treatment visits in order to maintain the blind.

Adolescents previously assigned to the placebo arm in the predecessor study

Adolescents previously assigned to the placebo arm in the predecessor study will be re-randomized to either the Q4W or Q8W regimen (first 3 doses administered every 4 weeks followed by every 8 weeks thereafter). Patients on the Q4W regimen will receive active drug every month. Patients on the Q8W regimen will receive active drug at Visit 1 (Week 0), Visit 2 (Week 4), Visit 3 (Week 8), followed by alternating monthly SC injections of placebo and active drug, eg, placebo at Visit 4 (Week 12), active drug at Visit 5 (Week 16), placebo at Visit 6 (Week 20), and so on in order to maintain the blind relative to the Q4W regimen.

Adolescents within the European Union (EU)

Adolescents previously assigned to an active treatment arm in the predecessor study

Adolescents within the EU will continue to receive only the Q8W dosing regimen as per the predecessor study. In order to maintain the blind of the predecessor study, this group will receive injections every 4 weeks for the first 3 doses (active drug at Visits 1 and 3, placebo administered at Visit 2) followed by every 8 weeks thereafter (to match the regimen of the adolescents who were on placebo in the predecessor study).

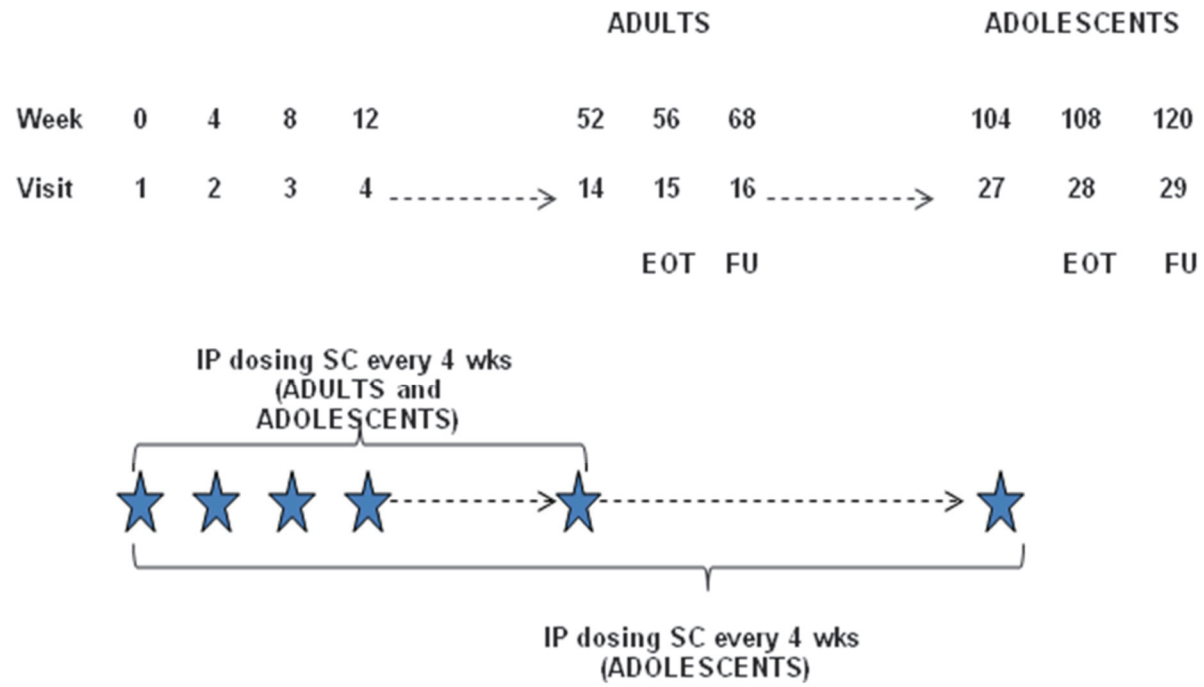
[2] For the purposes of this study the European Union (EU) is defined as consisting of the following countries: Bulgaria, Czech Republic, France, Germany, Italy, Poland, Romania, Spain, Sweden and the United Kingdom.

Adolescents previously assigned to the placebo arm in the predecessor study

Adolescents within the EU who were randomized to placebo in the predecessor study will be assigned to benralizumab 30 mg Q8W in this study (every 4 weeks for the first 3 doses followed by every 8 weeks thereafter).

After the first 3 doses, adolescent patients within the EU will be receiving open-label treatment with IP administered at their bimonthly visit; however, they will still follow an every 4 weeks study visit schedule (see Table of Assessments, Table 2).

Figure 1 Study flow chart



IP administration will be managed via an IVRS call at every dosing visit to ensure correct dosing schedule as follows:

- Previously on active treatment: benralizumab Q4W or Q8W. For the Q8W regimen, placebo will be given at the interim visits.
- Previously on placebo: benralizumab at Visits 1-3 (ie, Q4W for first 3 doses), followed by benralizumab Q4W or Q8W. For the Q8W regimen, placebo will be given at the interim visits.

NOTE: Adolescents on active treatment in the EU will continue on the Q8W regimen and will **not** receive placebo at the interim visits, except for Visit 2 (in order to maintain the blind). Adolescents in the EU on placebo will receive benralizumab at Visits 1-3 (ie, Q4W for first 3 doses), then continue on the Q8W regimen and will **not** receive placebo at the interim visits.

2. STUDY OBJECTIVES

(a) Primary Objective

Objective	Endpoint
1. To assess the safety and tolerability of 2 dosing regimens of benralizumab for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To assess the safety and tolerability of 2 dosing regimens of benralizumab for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• Number of AEs/SAEs • Laboratory variables • Physical examination

(b) Secondary Objectives

Objective	Endpoint
1. To evaluate the effect of 2 dosing regimens of benralizumab on asthma exacerbations in adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To evaluate the effect of 2 dosing regimens of benralizumab on asthma exacerbations in adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• Annual asthma exacerbation rate, where an asthma exacerbation is defined by a worsening of asthma requiring the use of systemic corticosteroids for at least 3 days, and/or an in-patient hospitalization, and/or an emergency department or urgent care visit.
1. To evaluate the effect of two dosing regimens of benralizumab on health care utilization and work and productivity loss for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To evaluate the effect of two dosing regimens of benralizumab on health care utilization and work and productivity loss for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• WPAI+CIQ • Hospitalizations, ED visits, urgent care visits and all other outpatient visits due to asthma

Objective	Endpoint
1. To assess the effect of 2 dosing regimens of benralizumab on asthma related and general health-related quality of life for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To assess the effect of 2 dosing regimens of benralizumab on asthma related and general health-related quality of life for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• AQLQ(S)+12 • EQ-5D-5L
1. To assess the effect two dosing regimens of benralizumab on asthma control for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To assess the effect two dosing regimens of benralizumab on asthma control for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• ACQ-6
1. To evaluate the pharmacokinetics and immunogenicity of 2 dosing regimens of benralizumab for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To evaluate the pharmacokinetics and immunogenicity of 2 dosing regimens of benralizumab for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• PK parameters • Anti-drug antibodies (ADA)

Objective	Endpoint
1. To assess the effect of 2 dosing regimens of benralizumab on pulmonary function for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To assess the effect of 2 dosing regimens of benralizumab on pulmonary function for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• Pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at the study center
1. To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• Blood eosinophils

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 (and/or assent as applicable locally) for study participation must be obtained prior to any study related procedures being performed (local regulations are to be followed in determining the assent/consent requirements for children and parent(s)/guardian(s)) and according to international guidelines and/or applicable European Union guidelines.

2. Female and male patients who completed the double-blind treatment period in a predecessor study on benralizumab or matching placebo.

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 postemenopausal if they have been amenorrheic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

– Women <50 years old 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 studies 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 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 a 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 a 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 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 major protocol deviations in any of the predecessor studies at the discretion of the Sponsor

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

3.3 Patient enrolment and randomization

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

The Investigator will:

1. Obtain signed informed consent and/or assent as applicable locally (hereafter referred to collectively as 'consent') from the patient, and/or parent or legal guardian, before any study specific procedures are performed at Visit 1
2. Assign each potential patient a unique enrolment number beginning with 'E# via interactive web/voice response system (IWRS/ IVRS)
3. Determine patient eligibility
4. Assign eligible patient a unique randomization code via IWRS/IVRS

For all adult patients and non-EU adolescent patients previously assigned to the placebo arm in the predecessor study, randomization in this safety extension study will be stratified by the

predecessor study. For patients from the predecessor studies D3250C00017 and D3250C00018, the randomization will be further stratified by age group (adults/adolescents). In addition, the adult patients will be also stratified by country. Specific information concerning the use of the IWRS/IVRS will be provided in the separate manual.

3.4 Procedures for handling incorrectly randomized patients

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

Where a patient does not meet all the eligibility criteria but is randomized 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 the concomitant treatments given during the study, with reason for the treatment, will be collected by the Investigator/authorized delegate at each visit (as shown in Table 1 and Table 2) and recorded in the eCRF. AstraZeneca will link the records for concomitant medications, medical and asthma history and adverse events from the predecessor study to those collected for this study to create a continuous record.

3.5.1.1 Background medication

Patients are required to remain on the same stable dose of background asthma medication as in the predecessor study in order not to confound the objectives of the study. If changing the background asthma medication is judged necessary by the Investigator, the study physician should be contacted for approval, the justification should be documented in the source, and the change of drugs or doses should be reflected in the eCRF.

3.5.1.2 Rescue medication

Salbutamol, albuterol, or levalbuterol may be used as rescue medication during the study in the event of a worsening of asthma symptoms. Patients who are already on nebulized SABA as rescue medication can continue their use throughout the study.

3.5.2 Restrictions

3.5.2.1 Asthma medication restrictions

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

Pre- and/or post-dose spirometry assessments will be performed at the study center at scheduled visits (see Table 1 and Table 2): restrictions to patient's background

asthma medication are required prior to the spirometry as described below (also see Section 5.1.2):

Treatment Visits 1–14 (Visits 1-27 for adolescents):

Twice daily ICS and LABA therapies should be withheld for 12- 24 hours; once daily therapies containing ICS, LABA, or LAMA therapies should be withheld for ≥24 hours before scheduled center visit spirometry as this will affect the pre-BD FEV_1 value; they may be taken subsequently, at the center. For the same reason patients should not use their rescue SABA medication (albuterol/salbutamol/levalbuterol) within 6 hours of a scheduled center visit spirometry. This restriction is particularly critical for efficacy measures taken during the treatment period.

If the patient has taken their usual ICS-LABA asthma controller medication on the morning of the scheduled spirometry visit, the Investigator/authorized delegate should remind the patient of the importance of withholding their usual morning asthma medication, and reschedule the visit for another day within the allowed window.

If the patient has taken rescue SABA within 6 hours of the planned center visit spirometry they should ideally

1) remain at the center until such time that the 6 hour withholding time has been reached if it does not exceed the 1.5 hour spirometry window or

2) return on another day, within the visit window.

(b) **Asthma medication restrictions on unscheduled visits**

Asthma medication restrictions on unscheduled visits may not be feasible and may be applied at the discretion of the Investigator. Timing of recent controller and rescue SABA use relative to the unscheduled spirometry should be noted in the record.

3.5.2.2 Other medication restrictions

(a) Use of immunosuppressive medication (other than prior stable oral corticosteroids for the maintenance treatment of asthma or bolus systemic steroids for the treatment of an asthma exacerbation) or administration of live/attenuated vaccines is not allowed. Topical administration of immunosuppressive medication and local corticosteroid injections may be allowed at the discretion of the Investigator after discussion with the AstraZeneca Study Physician.

(b) Patient should not receive an allergen immunotherapy injection on the same day as IP administration

(c) Patients who are on theophylline or digoxin; the Investigator should ensure the levels of each of these medications does not exceed the upper limit of therapeutic range. The Investigator will also be responsible for ensuring that these levels are regularly checked, assessed, and documented as per local practice

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

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

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

3.5.2.3 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 contraindicates further dosing
3. Risk to patient as judged by the Investigator or AstraZeneca
4. Severe non-compliance to study protocol
5. Eligibility requirement found not to be fulfilled (see Section 3.4)
6. Pregnancy
7. Lost to follow-up[3]
8. 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 or more than 2 scheduled doses of IP are missed during course of the study

[3] 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.

(d) An asthma-related event requiring mechanical ventilation

All patients who prematurely discontinue IP should return to the study center and complete the procedures described for the Premature Investigational Product Discontinuation Visit (IPD) within 4 weeks ±7 days after the last dose of IP and for the final Follow-up visit at 16 weeks (±7 days) after the last dose of IP (see Table 1 and Table 2).

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

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. Patients who discontinue IP will be discontinued from the study.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. The enrolment/randomization code of the withdrawn patient cannot be reused.

If patient agrees, he/she will be asked to return to the study center and complete procedures described for the IPD and FU visits within 4 weeks (+7 days) and 16 weeks (±7 days) after the last dose of IP, respectively.

3.8 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological 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.

As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

If the patient only withdraws consent for the retention of samples for future exploratory use, the patient will not be withdrawn from the study.

The Principal Investigator or designee:

- Ensures patients' withdrawal of informed consent for the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study center, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the local laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

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

4. STUDY PLAN AND PROCEDURES

Table 1 Study Assessments Schedule – Adults

Assessment/ activity	Refer to	Treatment														EOT [m]	IPD [j]	FU	UNS [i]
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15		V16	
		w0	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48	w52	w56		w68	
		Visit window (days) [c]																	
		±0	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	N/A
Inclusion/exclusion criteria	3.1/3.2	X																	
Informed consent	10.4	X																	
Medical and asthma history	5.2.1	X [a]																	
Comprehensive CV history [k]	5.2.1	X																	
Height	5.3.1	X [b]							X							X	X		
FSH [g]	5.2.5.1	X																	
Complete physical examination	5.2.2.1	X [b]														X	X		
Brief physical examination	5.2.2.2		X	X	X	X	X	X	X	X	X	X	X	X	X				X
Weight	5.3.1	X [b]							X							X	X		
Vital Signs	5.2.3	X [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Local ECG	5.2.4	X [b]							X							X	X		
Serum chemistry [d]	5.2.5	X [b]			X				X				X			X	X		
Hematology	5.2.5	X [b]			X				X				X			X	X	X	

Table 1 Study Assessments Schedule – Adults

Assessment/ activity	Refer to	Treatment														EOT [m]	IPD [j]	FU	UNS [i]
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15		V16	
		w0	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48	w52	w56		w68	
		Visit window (days) [c]																	
		±0	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	N/A
Urinalysis	5.2.5	X [b]			X				X				X			X	X		
Urine pregnancy test (dipstick) [e]	5.2.5.1	X [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK [f]	5.3.6	X [b]		X		X			X				X		X	X	X	X	
ADA/nAb [f]	5.3.7.1	X [b]		X		X			X				X		X	X	X	X	
ACQ-6	5.3.2.1	X [b]			X			X			X			X		X	X	X	
AQLQ(S)+12	5.3.2.2	X [b]			X			X			X			X		X	X	X	
WPAI+CIQ	5.3.2.3	X [b]																X	
EQ-5D-5L	5.3.2.4	X [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Health care resource utilization	5.3.3	X [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessment of asthma exacerbations	5.1.1	X [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pre- BD spirometry[l]	5.1.2	X [b]				X				X				X		X	X		X
Post- BD spirometry[l]	5.1.2	X [b]														X	X		
Randomization (where applicable)	6.5	X																	
Administration of IP [h]	6.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Adverse events	7	X [a]	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X

[a] Medical and asthma history, AEs and concomitant medications will be linked to the predecessor study to create a complete and continuous record for the patient.

[b] Assessments done at the EOT visit of the predecessor study do not need to be repeated at Visit 1 of this study, as the data will be duplicated between study databases (see Section 4.1.1).

[c] All visits are to be scheduled from the date of randomization but not from the date of previous visit

[d] Detailed schedule for serum chemistry tests provided in Section 5.2.5, Table 3 and Table 4

[e] For WOCBP, urine HCG test to be done at center on each treatment visit before IP administration.

[f] PK, ADA and nAb samples to be collected before IP administration.

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

[h] In case of anaphylaxis additional samples to be taken (see Section 6.9)

[i] Unscheduled visits may be initiated as needed, and additional assessments performed at these visits, at the discretion of the Investigator

[j] IPD visit should be completed within 4 weeks (+7 days) after last scheduled site visit

[k] Refer to CRF for specific CV history to be collected

[l] All patients transitioning from ZONDA into this study are exempt from performing the post-BD assessments. The pre-BD measurement from EOT for ZONDA patients will serve as the first pre-BD measurement for these patients in BORA.

m Patients transitioning into Study D3250C00037 will complete EOT assessments for this study at the same visit during which they transition. Patients who are asked to transition into this study by the Investigator must do so at the next odd-numbered visit (ie, Visit 5, 7, 9, or 11) once the study has started at their site (see Section 4.2).

D Days; EOT End-of-treatment; FU Follow-up; R Randomization; V Visit; UNS Unscheduled; W Week; IPD Premature IP Discontinuation

Table 2A Study Assessments Schedule – Adolescents: Weeks 0 to 64

Assessment/ activity	Refer to	Treatment																	IPD [i]	UNS [h]
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17		
		w0	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48	w52	w56	w60	w64		
		Visit window (days) [c]																		
		±0	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	+7	N/A
Inclusion/exclusion criteria	3.1/3.2	X																		
Informed consent+assent	10.4	X																		
Medical and asthma history	5.2.1	X [a]																		
Height	5.3.1	X [b]						X						X					X	
Complete physical examination	5.2.2.1	X [b]						X						X					X	
Brief physical examination	5.2.2.2		X	X	X	X	X		X	X	X	X	X		X	X	X	X		X
TBNK Flow Cytometry	5.3.5	X [b]			X				X				X			X			X	
Immunological Assessments	5.3.4.1	X [b]			X				X				X			X			X	
Weight	5.3.1	X [b]						X						X					X	
Vital Signs	5.2.3	X [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local ECG	5.2.4	X [b]							X							X			X	X
Serum chemistry [d]	5.2.5	X [b]			X				X				X			X			X	
Hematology	5.2.5	X [b]			X				X				X			X			X	
Urinalysis	5.2.5	X [b]			X				X				X			X			X	
Urine pregnancy	5.2.5.1	X [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 2A Study Assessments Schedule – Adolescents: Weeks 0 to 64

Assessment/ activity	Refer to	Treatment																	IPD [i]	UNS [h]
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17		
		w0	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48	w52	w56	w60	w64		
		Visit window (days) [c]																		
		±0	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	+7	N/A
test (dipstick) [e]																				
PK [f]	5.3.6	X [b]		X		X			X				X		X		X		X	
ADA/nAb [f]	5.3.7.1	X [b]		X		X			X				X		X		X		X	
ACQ-6	5.3.2.1	X [b]			X			X			X			X			X		X	
AQLQ(S)+12	5.3.2.2	X [b]			X			X			X			X			X		X	
WPAI+CIQ	5.3.2.3	X [b]														X			X	
EQ-5D-5L	5.3.2.4	X [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Health care resource utilization	5.3.3	X [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessment of asthma exacerbations	5.1.1	X [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pre- BD spirometry	5.1.2	X [b]				X				X				X				X	X	X
Post- BD spirometry	5.1.2	X [b]												X					X	
Randomization	6.5	X																		
Administration of IP [j]	6.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events	7	X [a]	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X

[a] Medical and asthma history, AEs and concomitant medications will be linked to the predecessor study to create a complete and continuous record for the patient.

[b] Assessments done at the EOT visit of the predecessor study do not need to be repeated at Visit 1 of this study, as the data will be duplicated between study databases (see Section 4.1.1).

[c] All visits are to be scheduled from the date of randomization but not from the date of previous visit

[d] Detailed schedule for serum chemistry tests provided in Section 5.2.5, Table 3 and Table 4

[e] For all adolescent females, urine HCG test to be done at center on each treatment visit before IP administration.

[f] PK, ADA and nAb samples to be collected before IP administration.

[g] In case of anaphylaxis additional samples to be taken (see Section 6.9)

[h] Unscheduled visits may be initiated as needed, and additional assessments performed at these visits, at the discretion of the Investigator

[i] IPD visit should be completed within 4 weeks (+7 days) after last scheduled site visit

[j] For adolescent patients in the EU, IP administration is Q4W for the first 3 doses (dummy injection of placebo for those patients on benralizumab in the predecessor studies) and then Q8W thereafter, with no injection of placebo at the 4 week interim visits.

D Days; EOT End-of-treatment; FU Follow-up; R Randomization; V Visit; UNS Unscheduled; W Week; IPD Premature IP Discontinuation

Table 2B Study Assessments Schedule – Adolescents: Weeks 68 to 120

Assessment/ activity	Refer to	Treatment										EOT	IPD [i]	FU	UNS [h]
		V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28		V29	
		w68	w72	w76	w80	w84	w88	w92	w96	w100	w104	w108		w120	
		Visit window (days) [c]													
		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	N/A
Height	5.3.1		X						X			X	X		
Complete physical examination	5.2.2.1		X						X			X	X		
Brief physical examination	5.2.2.2	X		X	X	X	X	X		X	X			X	X
TBNK Flow Cytometry	5.3.5			X				X				X	X	X	
Immunological Assessments	5.3.4.1			X				X				X	X	X	
Weight	5.3.1		X						X			X	X		
Vital Signs	5.2.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 2B Study Assessments Schedule – Adolescents: Weeks 68 to 120

Assessment/ activity	Refer to	Treatment										EOT	IPD [i]	FU	UNS [h]
		V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28		V29	
		w68	w72	w76	w80	w84	w88	w92	w96	w100	w104	w108		w120	
		Visit window (days) [c]													
		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	N/A
Local ECG	5.2.4					X						X	X		X
Serum chemistry [d]	5.2.5			X				X				X	X		
Hematology	5.2.5			X				X				X	X	X	
Urinalysis	5.2.5			X				X				X	X		
Urine pregnancy test (dipstick) [e]	5.2.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK [f]	5.3.6			X				X				X	X	X	
ADA/nAb [f]	5.3.7.1			X				X				X	X	X	
ACQ-6	5.3.2.1		X			X			X			X	X	X	
AQLQ(S)+12	5.3.2.2		X			X			X			X	X	X	
WPAI+CIQ	5.3.2.3											X	X		
EQ-5D-5L	5.3.2.4	X	X	X	X	X	X	X	X	X	X	X	X	X	
Health care resource utilization	5.3.3	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessment of asthma exacerbations	5.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pre- BD spirometry	5.1.2				X				X			X	X		X
Post- BD spirometry	5.1.2											X	X		
Administration of IP [g,j]	6.8	X	X	X	X	X	X	X	X	X	X				

Table 2B Study Assessments Schedule – Adolescents: Weeks 68 to 120

Assessment/ activity	Refer to	Treatment										EOT	IPD [i]	FU	UNS [h]
		V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28		V29	
		w68	w72	w76	w80	w84	w88	w92	w96	w100	w104	w108		w120	
		Visit window (days) [c]													
		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	N/A
Adverse events	7	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

[a] Medical and asthma history, AEs and concomitant medications will be linked to the predecessor study to create a complete and continuous record for the patient.

[b] Assessments done at the EOT visit of the predecessor study do not need to be repeated at Visit 1 of this study, as the data will be duplicated between study databases (see Section 4.1.1)

[c] All visits are to be scheduled from the date of randomization but not from the date of previous visit

[d] Detailed schedule for serum chemistry tests provided in Section 5.2.5, Table 3 and Table 4

[e] For all adolescent females, urine HCG test to be done at center on each treatment visit before IP administration.

[f] PK, ADA and nAb samples to be collected before IP administration.

[g] In case of anaphylaxis additional samples to be taken (see Section 6.9)

[h] Unscheduled visits may be initiated as needed, and additional assessments performed at these visits, at the discretion of the Investigator

[i] IPD visit should be completed within 4 weeks (+7 days) after last scheduled site visit

[j] For adolescent patients in the EU, IP administration is Q8W with no injection of placebo at the 4 week interim visits.

D Days; EOT End-of-treatment; FU Follow-up; R Randomization; V Visit; UNS Unscheduled; W Week; IPD Premature IP Discontinuation

4.1 Enrolment period

4.1.1 Randomization (Visit 1)

Each potential patient or parent/legal guardian (as applicable) will provide written informed consent prior to any study specific procedures and undergo assessments applicable for the visit (see Table 1 or Table 2).

In order to provide sufficient time for patients to consider participation in this study, and to ensure an uninterrupted dosing regimen as patients transition between the predecessor study and this study, patients will be provided with the ICF at/after the visit at which they receive their last dose of IP in the predecessor study and will be asked to sign the ICF at Visit 1 of this study, prior to any study-specific procedures being performed.

Visit 1 of this study will be scheduled to ensure an uninterrupted dosing regimen as patients transition between the predecessor study and this safety extension study. Therefore, if the actual EOT visit in the predecessor study occurs more than 7 days from the scheduled EOT visit, the patient will not be eligible to enrol in this study. The End-of-Treatment (EOT) visit for the predecessor study and Visit 1 for this study will occur on the same day and will include the first dose of IP for this study. If IP cannot be administered at this visit, the patient will not be eligible for enrolment in this study.

As Visit 1 coincides with the EOT visit of the predecessor study, repeated assessments (see Table 1 and Table 2) are not required, as data will be duplicated programmatically between the 2 study databases, as applicable As electronic patient-reported outcome (PRO) devices were used to capture ACQ6, AQLQ(S)+12, WPAI+CIQ, EQ-5D-5L in the predecessor studies, the patient does not need to complete the paper versions of these at Visit 1 of this safety extension study.

Registration of patient's enrolment via IWRS/IVRS should occur on day when other Visit 1 procedures are done.

Visit 1 assessments are primarily concerned with confirmation of the patient eligibility for the extension study

4.2 Randomized treatment period

4.2.1 Patients that continue for duration of BORA

Patients that will continue for the duration of BORA (comprising the first approximately 1200 adult patients enrolled in BORA), all patients in Japan and South Korea, and all adolescents will follow the procedures described below until completion of the study, or early withdrawal, as applicable.

4.2.2 Patients that will transition into MELTEMI

Patients who enter BORA after approximately 1200 adults have enrolled will be asked to transition into the separate safety extension study, MELTEMI, after completing a minimum of

16 weeks and a maximum of 40 weeks in BORA (ie, patients may transition at Visit 5, 7, 9, or 11).

Patients must transition from BORA into MELTEMI 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 is reached). Patients may transition into MELTEMI only at Visits 5, 7, 9, or 11 of this study.

4.2.3 Dosing regimens

4.2.3.1 Adults

Patients previously assigned to an active treatment arm in the predecessor study

Patients previously randomized to the Q4W regimen of benralizumab will continue injections of active drug every 4 weeks.

Patients previously randomized to the Q8W regimen will continue to receive active drug every 8 weeks with placebo (dummy) injections administered at the 4-week interim treatment visits in order to maintain the blind.

Patients previously assigned to the placebo arm in the predecessor study

All adult patients previously assigned to the placebo arm in the predecessor study will be re-randomized to either the Q4W or Q8W regimen (first 3 doses administered every 4 weeks followed by every 8 weeks thereafter). Patients on the Q4W regimen will receive active drug every month. Patients on the Q8W regimen will receive active drug at Visit 1 (Week 0), Visit 2 (Week 4), Visit 3 (Week 8), followed by alternating monthly SC injections of placebo and active drug, eg, placebo at Visit 4 (Week 12), active drug at Visit 5 (Week 16), placebo at Visit 6 (Week 20), and so on in order to maintain the blind relative to the Q4W regimen.

4.2.3.2 Adolescents outside the European Union

Adolescents previously assigned to an active treatment arm in the predecessor study

Adolescents previously randomized to the Q4W regimen of benralizumab will continue injections of active drug every 4 weeks.

Patients previously randomized to the Q8W regimen will continue to receive active drug every 8 weeks with placebo (dummy) injections administered at the 4-week interim treatment visits in order to maintain the blind.

Adolescents previously assigned to the placebo arm in the predecessor study

Adolescents previously assigned to the placebo arm in the predecessor study will be re-randomized to either the Q4W or Q8W regimen (first 3 doses administered every 4 weeks followed by every 8 weeks thereafter). Patients on the Q4W regimen will receive active drug

every 4 weeks. Patients on the Q8W regimen will receive active drug at Visit 1 (Week 0), Visit 2 (Week 4), Visit 3 (Week 8), followed by alternating monthly SC injections of placebo and active drug, eg, placebo at Visit 4 (Week 12), active drug at Visit 5 (Week 16), placebo at Visit 6 (Week 20), and so on in order to maintain the blind relative to the Q4W regimen.

4.2.3.3 Adolescents within the European Union

Adolescents previously assigned to an active treatment arm in the predecessor study

Adolescents within the European Union (EU) will continue to receive only the Q8W dosing regimen as per the predecessor study. In order to maintain the blind of the predecessor study, this group will receive the injections every 4 weeks for the first 3 doses (active drug at Visits 1 and 3, placebo administered at Visit 2) followed by every 8 weeks thereafter (to match the regimen of the adolescents who were on placebo in the predecessor study).

Adolescents within the EU will thereafter be receiving open label treatment. These adolescent patients will follow an every 4 weeks Study Visit schedule; however, investigational product (IP) will only be administered at every other visit after the first 3 doses as described above.

Adolescents previously assigned to the placebo arm in the predecessor study

Adolescents within the EU who were randomized to placebo in the predecessor study will be assigned to benralizumab 30 mg every 8 weeks in this safety extension study (every 4 weeks for the first 3 doses followed by every 8 weeks thereafter).

After the first 3 doses, adolescent patients within the EU will be receiving open label treatment with IP administered at their bimonthly visit.

With no placebo arm in this safety extension study, adolescent patients within the EU will thus be receiving open label treatment. These adolescent patients will follow an every 4 weeks Study Visit schedule; however, IP will only be administered at every other visit after the first 3 doses as described above.

4.2.3.4 Randomized treatment period assessments

For Visits 2 -16 (Visit 2 - 29 for adolescents), spirometry and blood sampling (for hematology, serum chemistry, PK, ADA/nAb) may be performed 1 day prior to the scheduled date of IP injection, at the discretion of the investigator. All other study procedures must be done on the scheduled day of IP injection. Urine pregnancy tests must be done prior to IP administration. The patient will receive 56 weeks treatment (108 weeks for adolescents), with the last dose of benralizumab administered at Visit 14 (Visit 27 for adolescents). Adolescent patients in EU will be administered IP according to open-label schedule.

Patients will have scheduled visits at 4-week intervals 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 an asthma worsening/exacerbation (see Section 5.1.1), patients should be evaluated at the study center,

when feasible, at an unscheduled visit, or ordinary visit if the worsening happens to fall within a scheduled visit window.

Patients' lung function will be monitored at the site, as well as responses to questionnaires (see Section 5.3.2 for details).

At Week 56 (Week 108 for adolescents) patients will come to the center for the End of Treatment (EOT) visit.

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 16 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 Visit 15, Week 56 (Visit 28, Week 108 for adolescents) will return at Week 68 (Week 120 for adolescents) for a final follow-up visit.

5. STUDY ASSESSMENTS AND PROCEDURES

5.1 Efficacy assessments

5.1.1 Assessment of asthma exacerbations

Although this is a safety study, asthma exacerbations will be assessed to characterize the exacerbation rate with longer maintenance treatment. In this study, an asthma exacerbation is defined as a worsening of asthma which requires use of systemic corticosteroids for at least 3 days, and/or an in-patient hospitalization, and/or emergency department or urgent care 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 counted as the same exacerbation event.

The patient may remain in the study after an exacerbation and continue to receive IP if the Investigator judges that it is medically appropriate for the patient to do so.

Study center evaluations for asthma worsening may occur as an unscheduled visit or as part of an ordinary center visit if the worsening happens to be coincident with a scheduled visit window. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study centers (eg, by the primary care HCP or at an emergency department/hospital) and details entered into the exacerbation eCRF in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the appropriate module of the eCRF.

5.1.2 Spirometry

General requirements

Lung function (FEV_1 and FVC) at the study center will be measured by spirometry using the site's own equipment. Spirometry will be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.(Miller et al 2005).

The Investigator is responsible for assuring that the spirometer used at the site meets ATS/ERS recommendations and that the study center personnel performing the testing are properly trained and certified. In order to minimize variability, the same spirometer should be used for all assessments of spirometry on patients in this study, wherever possible. If there is any need to change the device, AstraZeneca should be notified. Calibration of spirometers must be performed in accordance with the instructions of the manufacturer and should be performed every time a study subject visits the study center. All calibration reports must be signed, dated and filed in the Investigator Study File (ISF).

Important! Patients should withhold their usual ICS and long-acting bronchodilator containing medications on the morning of the Visit 1 FEV_1 measurement and post-bronchodilator testing. Twice daily ICS and long-acting bronchodilator therapies should be withheld for 12- 24 hours; once daily therapies containing ICS, LABA, or LAMA therapies should be withheld for ≥24 hours before scheduled center visit spirometry as this will affect the pre-BD FEV_1 value; they may be taken subsequently, at the center. For the same reason patients should not use their rescue SABA medication (albuterol/salbutamol/levalbuterol) within 6 hours of a scheduled center visit spirometry. This restriction is particularly critical for efficacy measures taken during the treatment period.

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

All patients transitioning from the OCS-sparing study (ZONDA) into this study are exempt from performing the post-BD assessments. The pre-BD measurement from EOT for ZONDA patients will serve as the first pre-BD measurement for these patients in BORA.

Time of day for scheduled center visit spirometry

Spirometry testing should be done according to the schedule provided in Table 1 or Table 2. All spirometry assessments should be performed within ±1.5 hours of the time that the first spirometry in the study (Visit 1) was performed. For example, if the first spirometry was started at 8:00 AM, then all subsequent spirometry testing should be initiated between 6:30 AM and 9:30 AM. Ideally, these assessments should be conducted at the same time of day as in the predecessor study, wherever possible.

Spirometry technique

Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Patients should avoid eating a large meal for at least 2 hours prior to spirometry

measurements at the center. Forced expiratory maneuvers should be performed with the patient seated in an upright position. If this is not comfortable for the patient, standing is permitted. The same position should be used by the patient for each forced expiratory maneuver from enrolment throughout the study. The head must not be tilted during maneuvers and the thorax should be able to move freely; hence tight clothing should be loosened. A nose-clip should be used for the maneuver. Disposable mouthpieces of the same dimension and shape should be used as far as possible for the duration of the study.

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

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each center spirometry session and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded. The best efforts will be based on the highest FEV_1. The absolute measurement (for FEV_1 and FVC), and the percentage of predicted normal value (Quanjer et al 2012) will be recorded. The highest FVC will also be reported regardless of the effort in which it occurred (even if the effort did not result in the highest FEV_1).

Post-bronchodilator spirometry

Post-BD spirometry will be performed as an efficacy measure on designated center visits during the treatment period as listed in Table 1 and Table 2.

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

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

Record keeping

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

Spirometry references

The Global Lung Function Initiative (GLI) equations will be used to determine the patient's predicted normal (PN) values (Quanjer et al 2012).

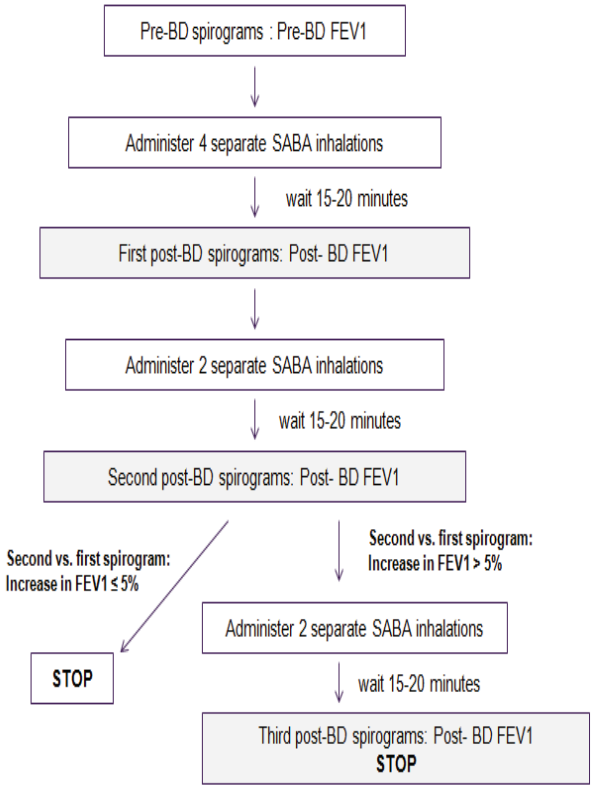
FEV_1 expressed as percent of the PN value will be calculated as follows:

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

5.1.2.1 Post-bronchodilator FEV_1 efficacy assessment

Post-bronchodilator (post-BD) spirometry will be performed as an efficacy measure on designated center visits during the treatment period as listed in Table 1 or Table 2. Maximal bronchodilatation should be induced using albuterol (90 µg metered dose), salbutamol (100 µg metered dose), or levalbuterol (45µg metered dose) up to a maximum of 8 inhalations (Sorkness et al 2008). It is highly recommended to use a spacer device for this procedure. The algorithm for testing is outlined in Figure 2.

Figure 2 Reversibility testing algorithm



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

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

3 Following this, an additional **2** inhalations of albuterol/salbutamol/ levalbuterol should be administered as single inhalations, 30 seconds apart (for a total of 6 inhalations). Second post-BD spirometry will be performed 15-20 minutes later.

4 If the incremental change in FEV_1 after 6 inhalations of albuterol/salbutamol/ levalbuterol is ≤5% of the FEV_1 value after 4 inhalations, the procedure is complete. If the change is >5% an additional 2 inhalations of albuterol/salbutamol/ levalbuterol should be administered in single inhalation 30 seconds apart and a third and final post-BD spirometry should be performed 15-20 minutes later.

A lower total dose, eg, 2 inhalations instead of 4 in the first round of puffs, and/or a total of less than 8 puffs, can be used if there is a concern about any effect on the patient's heart rate, tremor, or safety. Please note that the same procedure (ie, the same bronchodilator, device, number of puffs, etc.) should be used at all visits throughout the study.

The % difference comparing FEV_1 after 6 puffs to the FEV_1 after 4 puffs will be calculated as follows:

$$\% \text{ Difference} = FEV_1(6 \text{ puffs}) - FEV_1(4 \text{ puffs}) / FEV_1(4 \text{ puffs}) \times 100$$

5.2 Safety assessments

5.2.1 Medical and asthma history

Medical and asthma history will be retrieved from predecessor studies. Any new occurrence(s) or change(s) from previous status will be documented and if judged as clinically significant by the Investigator will be reported as an AE as described in Section 7. In addition, a detailed CV history will be taken at Visit 1.

5.2.2 Physical examination

Physical examination will be done in accordance with schedule provided in Table 1 or Table 2.

Baseline data will be collected at Visit 1. Any new finding(s) or aggravated existing finding(s) judged as clinically significant by the Investigator will be reported as an AE as described in Section 7.1.

5.2.2.1 Complete physical examination

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

5.2.2.2 Brief physical examination

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

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

Pulse rate, respiration rate, and blood pressure should be measured after the patient has been resting for at least 5 minutes. The measurement should be taken in sitting position.

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

5.2.4 Electrocardiogram

An electrocardiogram (ECG) will be performed in accordance with schedule provided in Table 1 or Table 2.

In all patients, the printouts of the ECG will be collected and signed, dated, and stored at the study center along with a signed and dated copy (if the printouts are not on archive-quality paper).

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

A standard ECG with a recommended paper speed of either 25 mm/second or 50 mm/second covering at least 6 sequential beats will be used. The Investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. In case of discrepancy between the Investigator's interpretation and that provided by the ECG machine (if applicable), the Investigator's interpretation will take precedence and should be noted on the printout and recorded in the eCRF. Two identical copies of the ECG will be produced and quality checked and kept in case of further need for re-evaluation.

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

ECG data and evaluation will be recorded in the eCRF.

5.2.5 Safety laboratory tests

Safety laboratory tests (list provided in Table 3 and Table 4) will be performed in a central laboratory. For information on methods of collection, assessment, labelling, storage and shipment of samples, please refer to the separate Laboratory Manual. Safety samples will be collected in accordance with the schedules provided in Table 1 or Table 2.

Hematology and urinalysis will be assessed in line with the schedules provided in Table 1 or Table 2. A detailed schedule of the chemistry tests is presented in Table 3 and Table 4. Visit 1 of this study is to be combined with the EOT visit of the predecessor study (see Section 4.1.1), therefore safety laboratory tests performed at the EOT visit in the predecessor study will be considered as baseline for this safety extension study. NB: As the required list of safety laboratory tests at Visit 1 of this safety extension study differs from those collected at EOT of the predecessor studies, the additional parameters required for this study (ie, those not required at the EOT visit of the predecessor study) will only be reported in this study to avoid duplicate reporting. Refer to the separate Laboratory Manual for more details.

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.

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

Table 3 List of safety laboratory tests

Serum chemistry		Hematology	Urinalysis
Alkaline phosphatase	Gamma-GT (gamma-glutamyl transpeptidase)	Hematocrit	Appearance
ALT (alanine aminotransferase)	Glucose	Hemoglobin	Blood
AST (aspartate aminotransferase)	Phosphorus	Mean corpuscular volume (MCV)	Colour
BUN (blood urea nitrogen)	Potassium	Platelet count	Glucose
Calcium	Sodium	Red blood cell (RBC) count	Ketones
Chloride	Total bilirubin	WBC count with differential[a]	Microscopy including WBC/high power field (HPF), RBC/HPF
CO2 (carbon dioxide)	Total cholesterol		pH
Creatinine	Uric acid		Specific gravity
Serum concentration [b]			

[a] Eosinophil, basophil and monocyte counts will be redacted from the central laboratory reports

[b] For patients who are on theophylline or digoxin (see Section 3.5.2.2)

Table 4 Serum chemistry tests schedule

VISIT	V1	V4	V8	V12	V15	V20 [a]	V24 [a]	V28 [a]
Alkaline phosphatase	X	X	X	X	X	X	X	X
ALT	X	X	X	X	X	X	X	X
AST	X	X	X	X	X	X	X	X
BUN	X	X	X	X	X	X	X	X
Calcium, serum	X	X			X			X
Chloride, serum	X	X			X			X
CO2 (carbon dioxide)	X	X			X			X
Creatinine	X	X	X	X	X	X	X	X
Gamma-GT	X	X	X	X	X	X	X	X
Glucose	X	X			X			X
Phosphorus, serum	X	X			X			X

Table 4 Serum chemistry tests schedule

VISIT	V1	V4	V8	V12	V15	V20 [a]	V24 [a]	V28 [a]
Potassium, serum	X	X			X			X
Sodium, serum	X	X			X			X
Total bilirubin	X	X	X	X	X	X	X	X
Total cholesterol	X	X			X			X
Uric acid	X	X			X			X

[a] Adolescents only

5.2.5.1 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 for all females (excluding adolescents) <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 including all adolescent females (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.

5.3 Other assessments and procedures

5.3.1 Weight and height

Weight and height will be measured in accordance with schedules provided in Table 1 or Table 2.

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

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

5.3.2 Patient reported outcomes

As part of routine monitoring of the patients' condition, patients will be asked about their asthma symptoms, rescue medication usage, nocturnal awakenings, and maintenance medication use at each visit or by phone between visits if they feel it is necessary. Patient reports will be verbal and no PRO instruments will be used for these assessments.

Background medication

Background asthma medication use will be recorded in the eCRF accordingly.

Patients will be requested to complete 4 simple questionnaires during particular visits as per Table 1 or Table 2, accordingly. Data will be collected using a paper form provided to the patient by the Investigator or designee at the time of visit.

5.3.2.1 Asthma Control Questionnaire

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

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

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤0.75 indicate well-controlled asthma, scores between 0.75 and ≤1.5 indicate partly controlled asthma, and a score >1.5 indicates not well controlled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered to be clinically meaningful.

The questionnaire will be completed by the patient at the site using a paper questionnaire.

Patients will be asked to complete the ACQ-6 at Visit 1 and then every 12 weeks thereafter throughout the treatment period including the EOT visit.

The Investigator/authorized delegate will check the patient's adherence to the ACQ-6, as shown in Table 1 or Table 2.

5.3.2.2 Standardised Asthma Quality of Life Questionnaire for 12 years and older

The Standardised Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12) is a questionnaire that measures the health-related quality of life experienced by asthma patients.

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

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

The questionnaire will be completed by patient at the site using a paper questionnaire.

Patients will be asked to complete the AQLQ(S)+12 at Visit 1 and then every 12 weeks thereafter throughout the treatment period including the EOT visit.

The Investigator/authorized delegate will check patient adherence to the AQLQ(S)+12 at each visit as shown in Table 1 or Table 2.

5.3.2.3 Work Productivity and Activity Impairment questionnaire plus Classroom Impairment Questions

The Work Productivity and Activity Impairment questionnaire plus Classroom Impairment Questions (WPAI+CIQ) questionnaire is a 10-item questionnaire that assesses productivity and activity impairment over the previous week. The questionnaire includes hours missed from work/school due to asthma, degree health affected productivity while at work/school, as well as the degree to which health affected regular activities other than work or school. The questionnaire relates to the previous 7 days.

The questionnaire will be completed by patients at the site using a paper questionnaire

Patients will be asked to complete the WPAI+CIQ at Visit 1 and at the EOT visit.

The Investigator/authorized delegate will check patient adherence to the WPAI+CIQ as shown in Table 1 or Table 2.

5.3.2.4 EQ-5D-5L

The EQ-5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty.

The patient will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the patient will be asked to rate current health status on a scale of 0-100, with 0 being the worst imaginable health state

The EQ-5D-5L will be completed at every scheduled visit.

The Investigator/authorized delegate will check patient adherence to the EQ-5D-5L at every scheduled visit as shown in Table 1 or Table 2.

5.3.3 Health care resource utilization

Information on the number of in-patient hospitalizations, number of days in the hospital, emergency department visits, urgent care visits and all other outpatient visits due to asthma 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.

Healthcare Resource Utilization (HRU) information will be collected with a recall period of ‘since the last scheduled visit’.

Healthcare Resource Utilization information will be completed at every scheduled visit.

Note: Cases of in-patient hospitalization also must be reported as an SAE (see Section 7.1.2 and 7.1.4).

5.3.4 Other assessments

5.3.4.1 Immunoglobulins for adolescents

The levels of total IgG, IgA, IgM, and IgE will be evaluated by a central laboratory. These tests will be performed at time points as specified in Table 2).

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

5.3.5 T cell, B cell, and NK cell flow cytometry for adolescents

T cell, B cell, and NK cell (TBNK) flow cytometry of whole blood will be evaluated by a central laboratory. This test will be performed at the visits as described in Table 2.

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

5.3.6 Pharmacokinetics

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

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

Serum will be collected pre-dose according to the schedule of study procedures (see Table 1 or Table 2).

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

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

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

5.3.7 Pharmacodynamics

5.3.7.1 Immunogenicity

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

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

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

ADA and nAb will be assessed using validated bioanalytical methods. Details of the analytical methods used will be described in separate bioanalytical reports.

Anti-benralizumab antibodies and neutralizing antibodies:

The pre-dose serum samples to measure presence of anti-benralizumab antibodies (ADA) will be collected according to the schedule of study procedures (see Table 1 or Table 2).

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

Neutralizing antibodies (nAb) are to be assessed at the time points as specified in Table 1 and Table 2. Samples that are ADA-negative will not be tested for nAb.

Astrazeneca will retain remaining serum supplies from samples designated for PK and ADA analyses for future asthma-related research. Any exploratory research performed after study completion will be asthma-related research only and may be limited by local restrictions. Serum samples will be retained for a maximum of 15 years following the Last Patient's Last Visit.

5.3.8 Handling of biological samples

5.3.8.1 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.

5.3.8.2 Chain of custody of biological samples

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

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

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

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

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

6. MANAGEMENT OF INVESTIGATIONAL PRODUCTS

6.1 Identity of investigational product(s)

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

Benralizumab and placebo administered in the study will be a clear to opalescent, colourless to yellow solution (Table 5).

Table 5 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
Placebo	Matching placebo 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/placebo is to be stored at the study center in a secured facility with limited access and controlled temperature. The temperature should be monitored on a daily basis and documented in the temperature monitoring log.

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

In the following cases:

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

the center staff should not use affected IP and should immediately contact an AstraZeneca representative for further guidance. Damaged IP should be documented via IWRS/IVRS (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 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 adults globally, and adolescents outside the EU who were randomized to benralizumab in the predecessor study will be assigned to the same dosing regimen in this safety extension study as they received in the predecessor study. Patients who were randomized to the placebo arm in the predecessor study will be randomized at Visit 1 of this safety extension study to 1 of the 2 benralizumab dose regimens (in a ratio of 1:1). Randomization codes will be assigned strictly sequentially as patients become eligible for randomization in accordance with stratification in this study. All adolescents within the EU will be assigned to the 30mg every 8 weeks dose regimen regardless of the treatment assignment in the lead-in study.

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

6.6 Methods for ensuring blinding

AstraZeneca staff involved in the study, the patients, and the investigators involved in the treatment of the patients, or in their clinical evaluation, will not be aware of the dosing regimen allocation, except in the case of adolescents within EU (who only receive the every 8 weeks dosing regimen, and who therefore will be on open label treatment in this study).

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

Center staff who are directly involved in the patient's management should remain blinded to any eosinophil, basophil, and monocyte results included as part of outside lab reports up to and including Visit 2 in order to maintain the blind of the predecessor study. To help ensure this, each investigational center will designate an individual (eg, administrator or another ancillary person) not directly involved in patient management, to receive and blind any eosinophil, basophil, and monocyte results prior to the report being handed over to the center staff involved in the patient's management and prior to filing as a source document. Similarly, eosinophil and basophil results must be redacted from all communications with the Sponsor.

After database lock has been declared in each of the predecessor studies (CALIMA, SIROCCO, and ZONDA), the treatment codes will be broken and the data from these studies will be analyzed and reported. Once the blind is broken in these studies, this study (BORA) becomes a single-blind design for those patients who had been on active treatment in the predecessor studies. The study will become single blind for all remaining patients at the time of the Japanese EOT analysis (see Section 8.5.4). While the Sponsor will be unblinded to regimen for analysis purposes, study conduct and blinding at the site and patient level will remain unchanged.

To prevent complete unblinding of this study, treatment-revealing information will not be shared with the study site or patients (patient-level listings, as well as other treatment-revealing information will be redacted from the Clinical Study Reports).

6.7 Methods for unblinding

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

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

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

To protect the blind of this study and of the predecessor studies (CALIMA, SIROCCO, and ZONDA), patients who transition from this study into Study D3250C00037 (MELTEMI) will be unblinded to treatment regimen only after signing the ICF for MELTEMI, at which point they will have exited BORA.

6.8 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 or more than 2 of the scheduled doses of IP are missed during course of the study the patient should be discontinued; please refer to Section 3.6.

If an Investigator decides to skip the IP administration due to exacerbations, the above rule does not apply.

Before investigational product administration

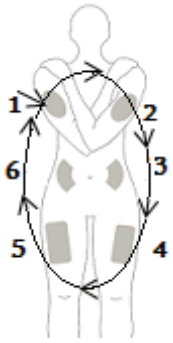
Prior to each IP administration:

- Investigator/authorized delegate will assess injection site as per standards of medical care
- For all WOCBP, including all adolescent females, a urine pregnancy test will be done. IP must only be administered when the result of the test is negative (see Section 5.2.5.1)

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

Figure 3 Injection sites and rotation scheme



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

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

After 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

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

In order to help understand the potential drug-relatedness of any acute reaction, a blood sample should be drawn during the event for 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 and including the follow-up period (Visit 16, Week 68 (Visit 29, Week 120 for adolescents). AEs, including SAEs that started during the predecessor

study and are ongoing at the start of this safety extension study, will be followed up for the duration of the study and as long as medically indicated.

7.1.3.2 Follow-up of unresolved adverse events

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

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

Any follow-up information of ongoing SAEs after database lock will be reported to AstraZeneca (see Section 7.1.4).

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 examinations and tests

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

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

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

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.

After randomization, asthma exacerbations should be recorded in the exacerbation eCRF (EXACA; see Section 5.1.1). If the exacerbation fulfils any of the above criteria, the sign or symptom should also be recorded as an AE.

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 randomized. Subsequent amendments will be documented ahead of database lock for the planned analyses (Section 8.5.4) if necessary.

8.2 Sample size estimate

Patients who complete the double-blind treatment period on IP in 1 of the predecessor studies, D3250C00017, D3250C00018, and D3250C00020, may be eligible to enrol into this study. With an estimated rollover rate of >90% from these preceding studies, this safety extension study will enrol approximately 1800 to 2000 patients, up to a maximum of 2200 patients worldwide. The first 1200 adult patients will remain in this study through IPD or EOT and FU. The remaining 700-1000 adult patients will be asked to transition into a safety extensions study, Study D3250C00037. Adolescent patients and patients from Japan and South Korea will remain in this study through IPD or EOT and FU.

A minimum of 1200 patients is considered sufficient to address the primary objective of safety and tolerability in the on-treatment and 16-week safety follow-up period of this study. The safety extension study, MELTEMI, will allow remaining patients to continue to receive benralizumab until it is available in their local market or until it has been withdrawn from the approval process in their local market. The minimum 16-week treatment period prior to transition to MELTEMI ensures that any patients previously randomized to placebo have completed monthly study visits and assessments for the first 3 active doses within this study before transitioning to MELTEMI.

The study is not designed to power the statistical testing of any null hypothesis.

8.3 Definitions of analysis sets

In the analysis sets outlined below, data from adult patients choosing to enter the safety extension study, D3250C00037, will be summarized separately from those remaining in this study (BORA) unless otherwise noted in the SAP.

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 randomized or assigned.

8.3.2 Pharmacokinetic analysis set

All patients who received benralizumab, from whom PK blood samples are assumed not to be affected by factors such as protocol violations, and who had at least 1 quantifiable serum PK

observation post first dose will be included in the PK analysis dataset. All PK summaries will be based on this analysis set.

8.4 Variables for analyses

8.4.1 Calculation or derivation of efficacy variables

All efficacy objectives will be evaluated for the treatment period, defined as the period after administration of IP at Visit 1 to the conclusion of the EOT visit, inclusive.

8.4.1.1 Exacerbation rate

The annual asthma exacerbation rate will be used as an efficacy variable.

An asthma exacerbation is defined in Section 5.1.1.

In order to calculate the number of exacerbations experienced by a patient during the treatment period, the following rule will be applied.

The start of an exacerbation is defined as the start date of systemic corticosteroids or start date of a temporary increase in a stable oral corticosteroid background dose, or start date of hospital admission, whichever occurs earlier. The end date is defined as the last day of systemic corticosteroids or the last day of a temporary increase in a stable oral corticosteroid background dose, or the date of discharge from a hospital, whichever occurs later. In the primary analysis, the number of exacerbations observed for a patient during the 56-week treatment period (108-weeks in adolescents) will be used as response variable.

Additional systemic corticosteroid treatments, emergency room /urgent care visits requiring use of systemic corticosteroids for at least 3 days, or in-patient hospitalization due to asthma occurring during an exacerbation should not be regarded as a new exacerbation. In order to be counted as a new exacerbation, it must be preceded by at least 7 days in which neither criterion is fulfilled.

Maximum on-treatment follow-up time for exacerbations for a patient is approximately 56 weeks (108 weeks for adolescents); defined as the time from first dose to the date of EOT. For a patient lost to follow-up, this will be defined as the time from randomization to the time point after which an exacerbation could not be assessed.

For the production of summary statistics, the annual exacerbation rate in each treatment group will be calculated using the time-based approach.

*Annual Exacerbation Rate=Total Number of Exacerbations*365.25/ Total duration of follow-up within the treatment group (days).*

8.4.1.2 Time to first exacerbation

Time to first exacerbation will only be calculated for the patients who were randomized to placebo in the lead-in study and is calculated as follows:

Start Date of first asthma exacerbation − Date of First Dose of Benralizumab + 1.

The time to first asthma exacerbation for patients who do not experience an asthma exacerbation during the treatment period will be censored at the date of their last visit for the treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients).

8.4.1.3 Forced expiratory volume in 1 second

The change from baseline to each of the post-randomization visits (post Visit 1 up to and including the EOT visit) will be used as secondary efficacy variables.

The last measurement recorded prior to the first dose (Visit 1) will be used as baseline FEV_1.

8.4.2 Calculation or derivation of safety variable(s)

8.4.2.1 Safety variables

The following safety data will be collected: vital signs, physical examination, 12-lead ECG, hematology, clinical chemistry, urinalysis, and reported AEs.

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

8.4.3 Calculation or derivation of patient reported outcome variables

8.4.3.1 Asthma Control Questionnaire

In the ACQ-6 questionnaire the subjects are asked to recall the status of their asthma during the previous week with regards to symptom and BD. The questionnaire includes questions on

- Awakened at night by symptoms
- Limitation of normal daily activities
- Waking in the morning with symptoms
- Dyspnoea
- Wheeze
- Daily rescue medication

The questions of the ACQ-6 are measured on a 7-point scale scored from 0 (totally controlled) to 6 (severely uncontrolled). The ACQ-6 score is computed as the un-weighted mean of the responses.

Asthma control responder status (Improved, No change, Deterioration) will be categorized according to the following limits (Juniper et al 2005):

- ACQ-6 (End of treatment – baseline) $\leq$-0.5 $\rightarrow$ Improvement
- -0.5< ACQ-6 (End of treatment– baseline) <0.5 $\rightarrow$ No change

- ACQ-6 (End of treatment– baseline) ≥0.5 → Deterioration

Asthma control status will be categorized according to their ACQ-6 end of treatment score as follows (Juniper et al 2006):

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

The primary outcome for those not previously treated with benralizumab in the predecessor study will be improvement from baseline (Visit 1) in asthma control as defined above. The primary outcome for those previously treated with benralizumab in the predecessor study will be maintenance of asthma control defined as either improvement or no change from baseline (Visit 1).

8.4.3.2 Standardised Asthma Quality of Life Questionnaire for 12 years and older

The AQLQ(s)+12 is a 32 question health-related quality of life assessment. Respondents are asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment).

The overall score is calculated as the mean response to all questions. The 4 individual domain scores (4 domains assessing 1) symptoms, 2) activity limitations, 3) emotional function, and 4) environmental stimuli) are the means of the responses to the questions in each of the domains. All patients will be categorized according to the following definitions:

- AQLQ(S)+12 (End of treatment – baseline) ≥0.5 → Improvement
- -0.5 < AQLQ(S)+12 (End of treatment – baseline) <0.5 → No change
- AQLQ(S)+12 (End of treatment – baseline) ≤-0.5 → Deterioration

The primary outcome for those not previously treated with benralizumab in the predecessor study will be improvement from baseline (Visit 1) as defined above. The primary outcome for those previously treated with benralizumab in the predecessor study will be maintenance of health-related quality of life defined as either improvement or no change from baseline (Visit 1).

8.4.3.3 Health Care Utilization and Work Productivity and Activity Impairment

The ten questions included in the WPAI+CIQ are as follows:

1 = currently employed (yes/no)
2 = hours missed work due to health problems
3 = hours missed work due to other reasons
4 = hours actually worked
5 = degree health affected productivity while working (0-10 scale, with 0 meaning no effect)
6 = attends class in an academic setting (yes/no)

7 = hours missed class due to health problems

8 = hours actually attended class

9 = degree health affected productivity while attending class (0-10 scale, with 0 meaning no effect)

10 = degree health affected regular activities (other than work or class) (0-10 scale, with 0 meaning no effect)

For the work related questions, the following calculations should be used to create the variables of interest:

- Number of work hours missed = Q2
- Absenteeism = Q2/(Q2+Q4)
- Presenteeism = Q5/10
- Work Productivity Loss = Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)]
- Activity Impairment = Q10/10

For the class-related questions, the following calculations should be used to create the variables of interest:

- Number of class hours missed = Q7
- Absenteeism = Q7/(Q7+Q8)
- Presenteeism = Q9/10
- Absenteeism+Presenteeism = Q7/(Q7+Q8)+[(1-Q7/(Q7+Q8))x(Q9/10)]
- Activity Impairment = Q10/10

The primary outcome for those not previously treated with benralizumab in the predecessor study will be reductions in the variables of interest described above (number of work/class hours missed, absenteeism, presenteeism, and work productivity loss and activity impairment) when comparing the values at the EOT to baseline (Visit 1). The primary outcome for those previously treated with benralizumab in the predecessor study will be no change in the variables of interest when comparing values at the EOT visit to baseline (Visit 1).

8.4.3.4 EQ-5D-5L

The distribution of responses for each of the five dimensions will be summarized by visit. The change from baseline (Visit 1) on the visual analogue scale will also be evaluated. The primary outcome for those not previously treated with benralizumab in the predecessor study will be a higher mean score on the visual analogue scale at the EOT visit compared with the baseline visit (Visit 1). The primary outcome for those previously treated with benralizumab in the predecessor study will be no change in mean scores on the visual analogue scale at the EOT visit compared to the baseline visit (Visit 1).

8.4.3.5 Health Care Utilization

The annual rates of health care utilization by type of health care encounter will be calculated for in-patient hospitalizations, emergency department visits/urgent care visits combined, unscheduled outpatient visits, and all of these healthcare encounters combined. The rates of health care encounters will be calculated in a manner similar to the calculation of the annual exacerbation rates defined in Section 5.1.1. The primary outcome for those previously treated with benralizumab in the predecessor study will be no change in the mean rate of healthcare encounters by type in this safety extension study compared to the mean rates of healthcare encounters by type among the benralizumab treated patients in the predecessor studies. The primary outcome for those not previously treated with benralizumab in the predecessor study will be mean rates of healthcare encounters by type comparable to the mean rates of healthcare encounters for those previously treated with benralizumab in the predecessor study.

8.4.4 Calculation or derivation of pharmacokinetic variables

Due to the limited sampling schedule, the PK assessment will be primarily based on the observed steady-state serum trough (predose) concentrations, C_{trough}.

8.4.5 Calculation or derivation of immunogenicity variables

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

8.5 Methods for statistical analyses

Data from adult patients choosing to enter the safety extension study, D3250C00037, will be summarized separately from those remaining in this study (BORA), unless otherwise noted in the SAP. Presentations will be provided for the overall population, adults, and adolescents separately. The details will be specified in the SAP.

8.5.1 Efficacy endpoints analysis method(s)

The efficacy endpoints in this study are:

- Change from baseline in pre-bronchodilator/post-bronchodilator FEV_1
- Annual exacerbation rate
- Time to the first asthma exacerbation
- Health care resource utilization
- ACQ-6
- AQLQ(S)+12
- WPAI+CIQ
- EQ-5D-5L

All efficacy endpoints will be summarized by treatment group and other group variables, which will be specified in the SAP.

8.5.1.1 Analysis methods for safety variables

AEs will be summarized by means of counts summaries by study period (treatment period and follow-up period). AEs will be listed for each patient and summarized by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by MedDRA. Laboratory safety variables will be summarized using standard summary statistics and plots as appropriate. Other safety variables will be summarized as appropriate. Further details will be provided in the SAP.

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

8.5.1.2 Analysis methods for pharmacokinetic variables

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

Benralizumab serum concentrations will be summarized using descriptive statistics at each visit by treatment group and other group variables.

8.5.1.3 Analysis method for immunogenicity variables

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

8.5.1.4 Analysis methods for healthcare utilization and patient reported outcomes

The ACQ-6 and AQLQ(s)+12 outcome variables for those not previously randomized to benralizumab in prior studies will be the change in scores (ACQ-6/AQLQ(s)+12 and domains) from baseline to Week 56/EOT (Week 108/EOT in adolescents). Baseline is defined as the Visit 1 observation in this study (pre-treatment for these patients). Additionally, subjects not previously randomized to benralizumab will be categorized by responder and control status at Week 56/EOT (Week 108/EOT in adolescents)（Juniper et al 2005; Juniper et al 2006).

The outcome variable for those previously treated with benralizumab in the predecessor study will be maintenance of asthma control status (ACQ-6) and health-related quality of life (AQLQ(s)+12) at Week 56/EOT (Week 108/EOT in adolescents). Maintenance of control status in these patients previously treated with benralizumab will be evaluated several ways:

(i) The proportion of those with improvement or no change in ACQ-6 score from baseline to Week 56/EOT (Week 108/EOT in adolescents) will be compared with the

proportion of those with deterioration from baseline at Week 56/EOT (Week 108/EOT in adolescents).

(ii) The proportion of those patients with improvement or no change in ACQ-6 score from baseline to Week 56/EOT (Week 108/EOT in adolescents) will be calculated for each baseline state (well, partially, not well controlled).

(iii) The proportion of post-baseline ACQ-6 observations indicating well controlled asthma will be calculated for those patients who are well controlled at baseline. Likewise, the proportion of post-baseline ACQ-6 observations indicating well or partially controlled asthma will be calculated for patients in those states at baseline and separately for those not well controlled at baseline.

Asthma control responder status (Improved, No change, Deterioration) will be categorized according to the following limits (Juniper et al 2005):

- ACQ-6 (End of treatment – baseline) $\leq$-0.5 $\rightarrow$ Improvement
- -0.5< ACQ-6 (End of treatment– baseline) <0.5 $\rightarrow$ No change
- ACQ-6 (End of treatment– baseline) $\geq$0.5 $\rightarrow$ Deterioration

Asthma control status will be categorized according to their ACQ-6 end of treatment score as follows (Juniper et al 2006):

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

To evaluate maintenance of HRQoL the proportion of those with improvement or no change in AQLQ(s)+12 total and domain scores from baseline to Week 56/EOT (Week 108/EOT in adolescents) will be calculated, as will the proportion of those with deterioration from baseline at Week 56/EOT (Week 108/EOT in adolescents). These descriptive statistics will be calculated for each ACQ-6 control category as defined previously.

Health-related quality of life responder status will be defined as (Juniper et al 1994):

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

For the ACQ-6, the distribution of patients who are well-controlled, partly controlled, and not well-controlled will be summarized descriptively for each of the visits in which the assessment was completed. The level of improvement based on the ACQ-6 and the AQLQ(S)+12 will also be summarized descriptively for each of the visits in which the assessment was completed.

For the EQ-5D-5L, the distribution of responses for each of the 5 dimensions assessed will be summarized by visit. The change from baseline (Visit 1) on the visual analogue scale will also be evaluated. The primary outcome for those not previously treated with benralizumab in the predecessor study will be a higher mean score on the visual analogue scale at the EOT visit compared to the baseline visit (Visit 1). The primary outcome for those previously treated with benralizumab in the predecessor study will be no change in mean scores on the visual analogue scale at the EOT visit compared to the baseline visit (Visit 1).

The mean rates of healthcare utilization by type of event (in-patient hospitalizations, emergency department visits/urgent care visits combined, unscheduled outpatient visits, and all unscheduled healthcare encounters will be summarized over the treatment period. The primary outcome for those previously treated with benralizumab in the predecessor study will be no change in the mean rate of healthcare encounters by type in this safety extension study compared with the mean rates of healthcare encounters by type among the benralizumab treated patients in the predecessor studies. The primary outcome for those not previously treated with benralizumab in the predecessor study will be mean rates of healthcare encounters by type comparable to the mean rates of healthcare encounters for those previously treated with benralizumab in the predecessor study.

The number and percentage of patients employed and attending classes will be summarized for Visit 1 and the EOT visit. The number of work hours missed and the number of class hours missed due to asthma as well as the 4 summary scores of absenteeism, presenteeism, absenteeism + presenteeism combined, and activity impairment will also be summarized for Visit 1 and the EOT visit. The primary outcome for those not previously treated with benralizumab in the predecessor study will be reductions in the variables of interest (number of work/class hours missed, absenteeism, presenteeism, and work productivity loss and activity impairment) when comparing the values at the EOT to baseline (Visit 1). The primary outcome for those previously treated with benralizumab in the predecessor study will be no change in the variables of interest when comparing values at the EOT visit to baseline (Visit 1).

8.5.2 Subgroup analysis

Details of the subgroup analyses will be provided in the SAP.

8.5.3 Sensitivity analysis

N/A

8.5.4 Interim analysis

Following analyses will be performed:

- *Japanese patients EOT analysis (Japanese patients only)*: Data cutoff for this analysis will be determined by the date at which the final Japanese patient completes the EOT visit.

- *Adult completion analysis of BORA*: This analysis will be conducted when all adult patients within BORA have completed the study, and the final adolescent patient has

completed the first 56 weeks of treatment within BORA. At this time, all of the study objectives related to adults will be fully addressed.

- *Adolescent completion analysis*: This analysis will be conducted when the final adolescent patient has completed BORA, and will be reported in an addendum report to the BORA CSR.

Full details of each analysis will be outlined in separate SAPs.

8.6 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.

8.7 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) is an independent expert advisory group commissioned and charged with the responsibility of evaluating cumulative safety and other clinical trial data at regular intervals and making appropriate recommendations based on the available data. The DSMB will function independently of all other individuals associated with the conduct of the studies, including the study sponsor, AstraZeneca. The committee will operate in accordance with a DSMB Charter.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study center personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol (CSP) and related documents with the investigational staff and also train them in any study specific procedures and WBDC, IWRS/IVRS, PROs, and other systems to be 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 Q4 2014 and to end by Q3 2018.

The study may be terminated at individual study centers if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely 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 AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Center.

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the 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/Assent 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/Assent 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/Assent 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/Assent 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, parent, or legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study (before any study procedures are performed) as per local requirements. The Informed Consent/Assent Form needs to be adjusted as per local requirements.
- Ensure each patient, parent, or legal guardian is notified that they are free to discontinue from the study at any time
- Ensure that each patient, parent, or legal guardian is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient, parent or legal guardian provides signed and dated Informed Consent/Assent before conducting any procedure specifically for the study. Local regulations are to be followed in determining the assent/consent requirements for children of different age groups.
- Ensure the original, signed Informed Consent/Assent 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/Assent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the Informed Consent/Assent 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, and assent where applicable, AstraZeneca and the study center's Ethics Committee are to approve the revised Informed Consent/Assent 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.

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Clinical Study Protocol Appendix B

Drug Substance	Benrzalizumab (MEDI-563)
Study Code	D3250C00021
Edition Number	1
Date	*20 June 2014*

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	D3250C00021
Edition Number	1
Date	*20 June 2014*

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 lATA 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	D3250C00021
Edition Number	1
Date	18 July 2014

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

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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).

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 for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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Clinical Study Protocol Appendix E

Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00021
Edition Number	1
Date	9 July 2014

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 likely allergen for that patient (minutes to several hours):

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

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

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

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

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

Immune Complex Disease

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

3. SIGNS AND SYMPTOMS AND MANAGEMENT OF ACUTE ANAPHYLAXIS

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

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

Other earlier or concomitant signs and symptoms can include:

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

4. MANAGEMENT OF ACUTE ANAPHYLAXIS

4.1 Immediate intervention

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

4.2 Possibly appropriate, subsequent measures depending on response to epinephrine

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

(b) Establish and maintain airway.

(c) Administer oxygen.

(d) Establish venous access.

(e) Normal saline IV for fluid replacement.

4.3 Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion.

(b) Consider H1 and H2 antihistamines.

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

(d) Consider systemic corticosteroids.

(e) Consider vasopressor (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 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	D3250C00021
Edition Number	2
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Appendix F
Restricted and prohibited medications

PROHIBITED AND RESTRICTED MEDICATIONS

Asthma medication restrictions

Table 1 Asthma medication restrictions

Medication	Prohibited/restricted	Details
Maintenance asthma controller medications containing a LABA and/or LAMA	Restricted only on days of scheduled clinic visits	Usual ICS-LABA/LAMA should not be taken prior to scheduled spirometry and ECG assessments (to be administered once assessments are completed)
Short acting beta-agonists (SABA)	Restricted only on days of scheduled clinic visits	SABA should not be used within 6 hours prior to scheduled spirometry and ECG assessments.
Zileuton	Prohibited	Not allowed 30 days prior to Visit 1;during treatment period

Other medication restrictions

Table 2 Other medication restrictions

Medication	Prohibited/restricted	Details
Live Attenuated Vaccines	Prohibited	Not allowed 30 days prior to randomization; during treatment period, and 16 weeks after the Last Dose
Inactive/killed vaccinations (e.g. inactive influenza)	Restricted	Allowed provided they are not administered within 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 intra-articular 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
Any immunomodulators or immunosuppressives – topical	Restricted	Topical administration of immunosuppressive medication may be allowed at the discretion of the Investigator after discussion with the AstraZeneca Study Physician
Blood products or immunoglobulin therapy	Prohibited	Not allowed 30 days prior to date of ICF; during treatment period
Any marketed (eg omalizumab) or investigational biologic treatment	Prohibited	Not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1; during treatment period; 4 months or 5 half-lives (whichever is longer) after the last dose of the investigational product
Other investigational Products (including investigational use of an approved drug)	Prohibited	Not allowed 30 Days or 5 Half Lives (whichever is longer) prior to Visit 1; 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; 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 treatment period
Non-selective oral or ophthalmic β-adrenergic antagonist (e.g. propranolol)	Prohibited	Patients currently using any non-selective oral or ophthalmic β-adrenergic antagonist at the time of enrolment are not eligible for the study. Not allowed during treatment period.