Revised Clinical Study Protocol

Drug Substance	Benralizumab (MEDI-563)
Study Code	
Edition Number	4.0
Date	16 March 2015

A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Asthmatic Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β2 Agonist (CALIMA)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative

_____ _____

Date

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

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
1	13 May 2014		
2	16 March 2015		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change
1	22 May 2014		
2	04 June 2014		
3	11 August 2014		

PROTOCOL SYNOPSIS

A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Asthmatic Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β2 Agonist (CALIMA)

International Co-ordinating Investigator or Principal Investigator or National Co-ordinating Investigator

J. Mark FitzGerald

Study centre(s) and number of patients planned

This study will be conducted worldwide in approximately 290 study centres. Target is to randomize 1296 patients.

Study period		**Phase of development**
Estimated date of first patient enrolled	Q3 2013	Phase 3
Estimated date of last patient completed	Q1 2016	

Objectives

(a) Primary Objective

Objective	Endpoint
To evaluate the effect of 2 dosing regimens of benralizumab on asthma exacerbations in patients on high-dose ICS-LABA with uncontrolled asthma	Annual asthma exacerbation rate, where an asthma exacerbation is defined by a worsening[1] of asthma requiring (see Section 5.1.1): • Use of systemic corticosteroids (or a temporary increase in a stable oral corticosteroid background dose) for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids • An emergency room/urgent care visit (defined as evaluation and treatment for < 24 hours in an ED or urgent care centre) due to asthma that required systemic corticosteroids (as per above) • An inpatient hospitalization due to asthma (defined as an admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours)

[1] For the purpose of the protocol, worsening of asthma is defined as new or increased symptoms and/or signs (examination or lung function) that can be either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (diary-driven). The ePRO device will be programmed to alert both the patient and study centre when certain pre-specified worsening thresholds are crossed including: decrease in morning peak flow ≥30% on at least 2 of 3 successive days compared with baseline (last 10 days of run-in), and/or a ≥50% increase in rescue medication or one new or additional nebulized β2 agonist on at least 2 of 3 successive days compared with the average use for the previous week, and/or nocturnal awakening due to asthma requiring rescue medication use for at least 2 of 3 successive nights, and/or; an increase in total asthma symptom score (the sum of day time [evening assessment] and night time [morning assessment] of at least 2 units above the run-in average (last 10 days of run-in), or the highest possible score (daily score of 6), on at least 2 of 3 successive days.

If an exacerbation event is not associated with deterioration in at least one of the pre-specified objective measurements, the Investigator will have to justify the decision for defining the event as an exacerbation. Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

(b) Secondary Objectives

Objective	Endpoint
To assess the effect of 2 dosing regimens of benralizumab on pulmonary function	pre-bronchodilator FEV_1[a] and post-bronchodilator FEV_1 at the study centre
To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics (as per the ePRO)	• Asthma symptom score (total[a], daytime, and night time) • Rescue medication use • Home lung function (morning and evening PEF) • Nights with awakening due to asthma • ACQ-6
To assess the effect of 2 dosing regimens of benralizumab on other parameters associated with asthma exacerbations	Time to first asthma exacerbation and proportion of patients with ≥1 asthma exacerbation
To assess the effect of 2 dosing regimens of benralizumab on asthma related and general health-related quality of life	• AQLQ(S)+12 • EQ-5D-5L
To assess the effect of 2 dosing regimens of benralizumab on emergency room/urgent care visits and hospitalizations due to asthma	Annual rate of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalization
To evaluate the effect of 2 dosing regimens of benralizumab on health care resource utilization and productivity loss due to asthma	• WPAI+CIQ • Asthma specific resource utilization (eg, unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications)
To evaluate the pharmacokinetics and immunogenicity of 2 dosing regimens of benralizumab	• PK parameters • Anti-drug antibodies (ADA)
To evaluate the overall response to treatment	• CGIC • PGIC

[a] Key secondary efficacy endpoints

(c) Safety Objective

Objective	Endpoint
To assess the safety and tolerability of 2 dosing regimens of benralizumab	• AE/SAE • Laboratory variables • ECG • Physical Examination

(d) Exploratory Objectives

Objective	Endpoint
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels	Blood eosinophils
To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers	Serum biomarkers

Study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate the efficacy and safety of a fixed 30mg dose of benralizumab administered subcutaneously in patients with a history of asthma exacerbations and uncontrolled asthma receiving inhaled corticosteroid plus long-acting β_2-agonist (ICS-LABA) with or without oral corticosteroids (OCS) and additional asthma controllers.

Approximately 1296 patients will be randomized globally. Patients will be stratified by ICS dose at Visit 1 (high/medium), geographical region, age group (adult or adolescent), and peripheral blood eosinophil count at time of Visit 1 (<300 or ≥300 cell/μL).

Adult patients and adolescent patients in Rest of the World non-European Union countries (RoW, non-EU countries) will receive either placebo or one of the following regimens of benralizumab, those being every 4 weeks throughout the treatment period versus every 4 weeks for the first 3 doses followed by every 8 weeks thereafter.

Adolescent patients in European Union (EU) countries will be randomized to either placebo or benralizumab arm with first 3 doses administered every 4 weeks and followed by every 8-week dosing thereafter. These patients will still follow an every 4-week Study Visit schedule even though investigational product (IP) will only be given every other visit after the first 3 monthly doses.

After enrolment and confirmation of entry criteria, patients will proceed to screening/run-in period of a minimum 2 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Patients who meet eligibility criteria will be randomized to a 56-week treatment

period. Patients will be maintained on their currently prescribed ICS-LABA therapy(ies), without change, from enrolment throughout the run-in and treatment period. A follow-up visit will be conducted at Week 60 unless the patient is eligible for and decides to continue into a separate follow-on extension study. Patients who remain on IP for the double-blind treatment period as defined in the protocol may be eligible to enrol in the follow-on extension study.

Target patient population

Male and female adult and adolescent patients 12-75 years of age with asthma inadequately controlled by treatment with ICS-LABA with or without OCS or other asthma controller medications.

Investigational product, dosage and mode of administration

Benralizumab 30mg/mL solution for injection in an accessorized pre-filled syringe (PFS) will be administered at the study centre subcutaneously every 4 weeks for the first 3 doses and then every 4 or 8 weeks thereafter.

Comparator, dosage and mode of administration

For adults and adolescent patients in RoW, benralizumab or matching placebo solution for injection in an accessorized PFS will be administered at study site subcutaneously every 4 weeks.

For adolescents in EU, benralizumab or matching placebo solution for injection in an accessorized PFS will be administered at study site subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks.

Duration of treatment

Following enrolment at Week –4, the patient will enter a minimum 2-week screening/run-in period followed by a 56-week double-blind, randomized treatment period, with last dose of benralizumab/placebo administered at either Week 48 or Week 52, depending upon the treatment regimen assigned to the patient. End of treatment (EOT) visit will be conducted on Week 56. A follow-up visit will be conducted at Week 60.

The total planned study duration is 64 weeks.

Patients who remain on IP for the double-blind treatment period as defined in the protocol may be eligible to enrol in the follow-on extension study.

Statistical methods

The primary efficacy variable is the annual asthma exacerbation rate. Exacerbation rate in each of the 2 benralizumab dose regimen groups will be compared to exacerbation rate in the placebo group using a negative binomial model including covariates of treatment group, country, number of exacerbations in the year before the study, and the use of maintenance OCS (yes/no). The logarithm of the follow-up time will be used as an offset variable in the model. Change from baseline in pre-bronchodilator forced expiratory volume in 1 second

(pre-BD FEV_1) at Week 56 will be compared between each of the 2 benralizumab dose regimen groups and placebo using a repeated measures analysis. Treatment group will be fitted as the explanatory variable, and country, baseline pre-BD FEV_1, and the use of maintenance OCS (yes/no) will be fitted as covariates. Visit will be fitted as a categorical variable. Change from baseline in asthma symptom total score at Week 56 will be analyzed using a similar model as the model for change from baseline in pre-BD FEV_1. The primary endpoint and the 2 key secondary endpoints (change from baseline in pre-BD FEV_1 and asthma symptom total score at Week 56) will be analyzed primarily using the high-dose-ICS patients with baseline blood eosinophil counts ≥300/μL in full analysis set. Full analysis set includes all randomized patients who received any dose of IP. In addition, the exacerbation rate and the two key secondary endpoints will also be summarized in patients with baseline blood eosinophil counts <300/μL, <150/μL, 150-299/μL, 300-449/μL and ≥450/μL separately for descriptive purposes only. All the analyses will also be performed for the medium-dose-ICS patients and the combined population of high-dose-ICS and medium-dose-ICS patients.

Multiplicity will be adjusted for the primary endpoint and the 2 key secondary endpoints on the analysis of high-dose-ICS patients with baseline blood eosinophils ≥300/μL according to a gate-keeping procedure (see Section 8.5).

The study will recruit patients with blood eosinophil counts ≥300/μL and <300/μL at a ratio of about 2:1 and the study is powered for the primary efficacy analysis of the high-dose-ICS patients with blood eosinophils ≥300/μL. For the primary endpoint annual asthma exacerbation rate, around 228 adult and adolescent high-dose-ICS patients with baseline blood eosinophil counts ≥300/μL per treatment arm (approximately 684 total) will need to be randomized to achieve 90% power of detecting a 40% reduction in both benralizumab dose regimens versus placebo after multiplicity adjustment. This calculation has assumed two-sided 4% alpha level tests and an annual placebo rate of 0.88 events/patient. Sample size calculation is based on simulation and the negative binomial shape parameter is assumed to be 0.9. According to the 2:1 ratio, the study will also enrol around 114 high-dose-ICS patients/arm (approximately 342 total) with baseline blood eosinophil counts <300/μL. In addition it is expected that approximately 270 medium-dose-ICS patients (around 60 patients with eosinophil counts ≥300/μL and around 30 patients with eosinophil counts <300/μL per arm) will be recruited. So a total of around 1296 patients are expected to be randomized in the study.

The efficacy analyses will comprise both adults and adolescent patients.

There is no unblinded data review planned for this study. A blinded estimate of the overall exacerbation rate and shape parameter will be conducted before the last high-dose-ICS patient with eosinophil counts ≥300/μL is randomized. The review may result in an adjustment on sample size.

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

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AQLQ(S)+12	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
CGIC	Clinician Global Impression of Change
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
ePRO	Electronic patient reported outcome

Abbreviation or special term	Explanation
EU	European Union
EXACA	Exacerbation eCRF
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
Gamma-GT	Gamma-glutamyl transpeptidase
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 Utilisation
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 IP Discontinuation
IRB	Institutional Review Board
ISF	Investigator Study File
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System

Abbreviation or special term	Explanation
LABA	Long-acting β_2 agonists
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
OAE	Other significant adverse event
OCS	Oral corticosteroids
PEF	Peak expiratory flow
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic(s)
PN	Predicted normal
Post-BD	Post-bronchodilator
Pre-BD	Pre-bronchodilator
PRO	Patient reported outcome
RoW	Rest of the 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
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 step-wise intensification of a daily maintenance regimen primarily centred around ICS and leukotriene receptor antagonists (LTRA), with the addition of LABA in patients with more severe asthma (GINA 2011, NAEPP 2007). Despite treatment per management guidelines, up to 50% of patients have asthma that is not well-controlled (Bateman et al 2010). This results in considerable impact on quality of life, disproportionate use of healthcare resources, and adverse reactions from regular systemic steroid use. 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 2011). 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). 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 magnitude of clinical improvement was positively correlated with baseline blood eosinophil counts and was most consistently observed in patients with absolute blood eosinophil counts ≥300/μL. The purpose of this trial is to confirm the safety and clinical benefit of benralizumab administration in asthma patients who are otherwise uncontrolled on current standard of care therapy. The question of the baseline blood eosinophil level that predictably ensures the benefit will also be addressed in the study by inclusion of patients with blood eosinophil counts ≥300/μL and <300/μL.

1.3 Rationale for study design, doses and control groups

This is a global study designed to investigate the safety and efficacy of the fixed dose benralizumab (30mg) administered subcutaneously (SC) using 2 dosing regimens (every 4 weeks throughout the treatment period, versus every 4 weeks for the first 3 doses and then every 8 weeks thereafter), in exacerbation-prone asthma patients who remain uncontrolled on ICS-LABA with or without OCS and other asthma controller(s).

In adolescents in EU countries, the dose group being studied is being limited to benralizumab 30mg administered subcutaneously every 4 weeks for the first 3 doses followed by every 8 weeks thereafter. This is to accommodate the Paediatric Committee (PDCO) at the European Medicines Agency's request to limit drug burden in adolescents and so study only the less frequent dose.

Primary efficacy will be determined based on reduction in the rate of asthma exacerbations over 56 weeks for benralizumab versus placebo. In order to avoid biasing the results, the study will be randomized with stratification factors of ICS dose at Visit 1 (high/medium), geographical region, age group (adult or adolescent), and peripheral blood eosinophil count at time of Visit 1 (<300 or ≥300 cell/μL).The study will recruit patients with screening blood eosinophils ≥300/μL and <300/μL at a ratio of about 2:1. The 2:1 stratification of patients with eosinophil counts ≥300/μL and <300/μL is intended as a means of enriching the population for patients most likely to respond to benralizumab (ie, ≥300/μL), while still accommodating patients below this threshold in order to help understand where additional benefit drops off.

The benralizumab dose (30 mg SC, fixed) and the maintenance regimens are based on all available safety, efficacy and immunogenicity data, as well as population exposure-response modeling, and stochastic trial simulations from earlier phase benralizumab trials. In particular, showed that fixed doses of benralizumab ≥20 mg administered every 8 weeks were clinically effective. The potential impact on efficacy of anti-drug antibodies (ADA) and body weight on pharmacokinetics (PK) were incorporated in a population PK model. Analyses of efficacy endpoints (asthma exacerbations, FEV_1 and ACQ) suggest 30 mg every 8 weeks (with the first 3 doses administered every 4 weeks) is an effective and tolerable dose for further testing in patients with severe asthma. This dose corresponds to the ED_{90} (benralizumab dose corresponding to 90% of maximum efficacy) for asthma exacerbation reduction and ACQ, and maintains a steady-state PK exposure close to EC_{90} levels for FEV_1 and ACQ. Because the development of ADA to biologic products appears to be related to the consistency of exposure, a second, more frequent (every 4 weeks) dosing regimen will also be tested.

Asthma manifestations and responses to existing treatments in adolescents and adults are similar. With a 40 kg lower body weight limit, the projected PK exposure in adolescents mostly overlaps with that in adults. The PK difference between adolescents and adults is expected to be small and within the normal range of between-patient variability among adults. Further, the 100 mg Q8W top dose investigated in Phase 2b study provided adequate exposure coverage. To date, there are no data suggesting a dose- or exposure-related increase in Treatment Emergent Adverse Events (TEAE) with benralizumab in adult patients. As such adolescents (≥40kg) will receive 30 mg adult dose in Phase 3 studies.

Other stable asthma therapies on top of ICS-LABA that are within expert guidance and that are not restricted per protocol (see Section 3.5.2) are allowed in order to accommodate local standards of care.

1.4 Benefit/risk and ethical assessment

There are few treatment options for patients whose asthma remains uncontrolled on high-dose ICS-LABA (GINA 2011). The evidence base for oral add-on therapies (ie, OCS, 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 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, and will be explored in this study. Development of ADA to benralizumab has been documented. Theoretical risks of developing ADA include decreased drug efficacy and hypersensitivity reactions (eg, anaphylaxis or immune complex disease).

Eosinophils are a prominent feature of the inflammatory response to helminthic parasitic infections, and the presence of infiltrating eosinophils has been circumstantially associated with a positive prognosis in certain solid tumors. Therefore, there is a theoretical risk that prolonged eosinophil depletion may diminish the ability to defend against helminthic parasites, or negatively impact the natural history of certain malignant tumors. Risk minimization measures include exclusion of patients with untreated parasitic infection and active or recent malignancy, in conjunction with the performance of routine pharmacovigilance activities.

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

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

1.5 Overall study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate the efficacy and safety of a fixed 30mg dose of benralizumab administered subcutaneously in patients with a history of asthma exacerbations and uncontrolled asthma receiving ICS-LABA with or without OCS and additional asthma controllers.

Adult patients and adolescent patients in RoW will be randomized to either placebo or one of two dosing regimens of benralizumab, those being every 4 weeks throughout the treatment period versus every 4 weeks for the first 3 doses followed by every 8 weeks thereafter.

Adolescent patients in EU countries will be randomized to either placebo or benralizumab arm with first 3 doses administered every 4 weeks and followed by every 8-week dosing thereafter. These patients will still follow an every 4- week Study Visit schedule even though IP will only be given every other visit after the first 3 monthly doses.

The study will recruit approximately 1296 patients stratified by ICS dose at Visit 1 (high/medium), geographical region, age group (adult or adolescent), and peripheral blood eosinophil count at time of Visit 1(≥300/μL and <300/μL):

- Adult patients will be randomized in a 1:1:1 ratio and stratified by ICS dose (high/medium), country and eosinophil count ≥300/μL and <300/μL.
- Adolescent patients will be stratified by ICS dose (high/medium), region (EU/RoW) and eosinophil count ≥300/μL and <300/μL.

For details on strata closure procedures please refer to Section 3.7.2.

After enrolment and confirmation of entry criteria, patients will proceed to screening/run-in period of a minimum 2 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Patients who meet eligibility criteria will be randomized to a 56-week treatment period. Patients will be maintained on their currently prescribed ICS-LABA therapy(ies), without change, from enrolment throughout the run-in and treatment period. A follow-up visit will be conducted at Week 60 unless the patient is eligible for and decides to continue into a separate follow-on extension study. Patients who remain on IP for the double-blind treatment period as defined in the protocol may be eligible to enrol in the follow-on extension study.

Figure 1 Study flow chart for adult patients and adolescent patients in RoW non-EU countries

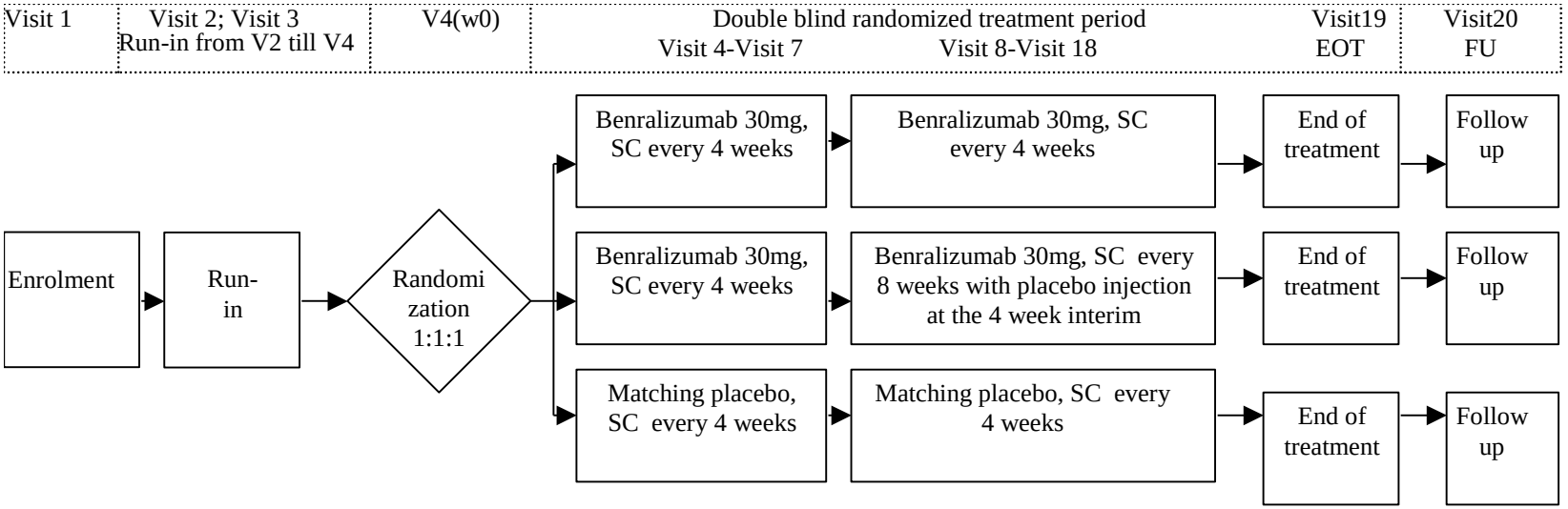
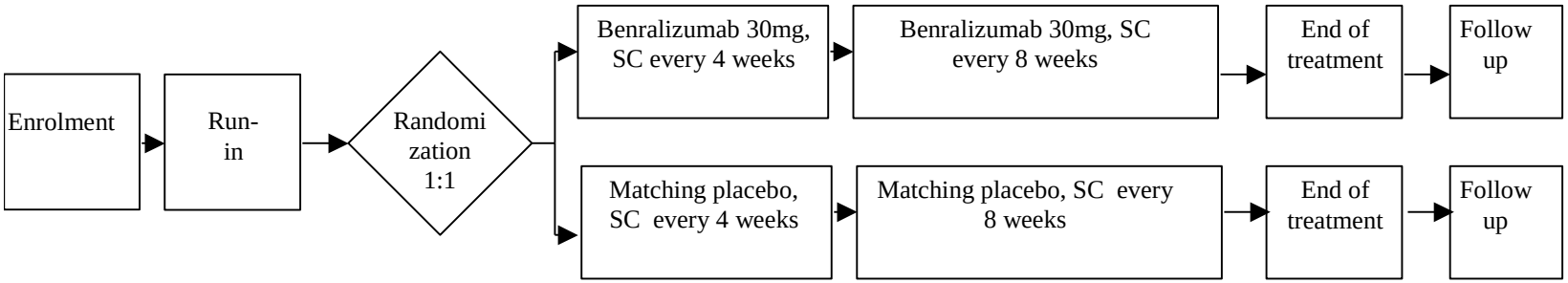


Figure 2 Study flow chart for adolescent patients in EU countries

Visit 1	Visit 2; Visit 3 Run-in from V2 till V4	V4(w0)	Double blind randomized treatment period Visit 4-Visit 7 Visit 8-Visit 18	Visit19 EOT	Visit20 FU



2. STUDY OBJECTIVES

(a) Primary Objective

Objective	Endpoint
To evaluate the effect of 2 dosing regimens of benralizumab on asthma exacerbations in patients on high-dose ICS-LABA with uncontrolled asthma	Annual asthma exacerbation rate, where an asthma exacerbation is defined by a worsening [2]of asthma requiring (see Section 5.1.1): • Use of systemic corticosteroids (or a temporary increase in a stable oral corticosteroid background dose) for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids • An emergency room/urgent care visit (defined as evaluation and treatment for < 24 hours in an ED or urgent care centre) due to asthma that required systemic corticosteroids (as per above) • An inpatient hospitalization due to asthma (defined as an admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours)

[2] For the purpose of the protocol, worsening of asthma is defined as new or increased symptoms and/or signs (examination or lung function) that can be either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (diary-driven). The ePRO device will be programmed to alert both the patient and study centre when certain pre-specified worsening thresholds are crossed including: decrease in morning peak flow ≥30% on at least 2 of 3 successive days compared with baseline (last 10 days of run-in), and/or a ≥50% increase in rescue medication or one new or additional nebulized β2 agonist on at least 2 of 3 successive days compared with the average use for the previous week, and/or nocturnal awakening due to asthma requiring rescue medication use for at least 2 of 3 successive nights, and/or; an increase in total asthma symptom score (the sum of day time [evening assessment] and night time [morning assessment] of at least 2 units above the run-in average (last 10 days of run-in), or the highest possible score (daily score of 6), on at least 2 of 3 successive days.

If an exacerbation event is not associated with deterioration in at least one of the pre-specified objective measurements, the Investigator will have to justify the decision for defining the event as an exacerbation. Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

(b) Secondary Objectives

Objective	Endpoint
To assess the effect of 2 dosing regimens of benralizumab on pulmonary function	pre-bronchodilator FEV_1[a] and post-bronchodilator FEV_1 at the study centre
To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics (as per the ePRO)	• Asthma symptom score (total[a], daytime, and night time) • Rescue medication use • Home lung function (morning and evening PEF) • Nights with awakening due to asthma • ACQ-6
To assess the effect of 2 dosing regimens of benralizumab on other parameters associated with asthma exacerbations	Time to first asthma exacerbation and proportion of patients with ≥1 asthma exacerbation
To assess the effect of 2 dosing regimens of benralizumab on asthma related and general health-related quality of life	• AQLQ(S)+12 • EQ-5D-5L
To assess the effect of 2 dosing regimens of benralizumab on emergency room /urgent care visits and hospitalizations due to asthma	Annual rate of asthma exacerbations that are associated with an emergency room /urgent care visit or a hospitalization
To evaluate the effect of 2 dosing regimens of benralizumab on health care resource utilization and productivity loss due to asthma	• WPAI+CIQ • Asthma specific resource utilization (eg, unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications)
To evaluate the pharmacokinetics and immunogenicity of 2 dosing regimens of benralizumab	• PK parameters • Anti-drug antibodies (ADA)
To evaluate the overall response to treatment	• CGIC • PGIC

[a] Key secondary efficacy endpoints

(c) Safety Objective

Objective	Endpoint
To assess the safety and tolerability of 2 dosing regimens of benralizumab	• AE/SAE • Laboratory variables • ECG • Physical Examination

(d) Exploratory Objectives

Objective	Endpoint
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels	Blood eosinophils
To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers	Serum biomarkers

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. Written informed consent, and assent when applicable, 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 aged 12 to 75 years, inclusively, at the time of Visit 1.

   – For those patients, who are 17 on the day of Visit 1 but will turn 18 after this day, will be considered an adolescent for the purposes of this trial.

3. Women of childbearing potential (WOCBP) (after menarche) must use a highly effective form of birth control (confirmed by the Investigator). Highly effective forms of birth control includes: true sexual abstinence, a vasectomised sexual partner, Implanon, female sterilization by tubal occlusion, any effective IUD Intrauterine device/IUS Ievonorgestrel Intrauterine system, , oral contraceptive, and WOCBP must agree to use highly effective method of birth control, as defined above, from

enrolment, throughout the study duration and within 16 weeks after last dose of IP, and have negative serum pregnancy test result on Visit 1.

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

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

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

4. All male patients who are sexually active must agree to use a double barrier method of contraception (condom with spermicide) from the first dose of IP until 16 weeks after their last dose

5. Weight of ≥40 kg

6. History of physician-diagnosed asthma requiring treatment with medium-to-high dose ICS (>250µg fluticasone dry powder formulation equivalents total daily dose) and a LABA, for at least 12 months prior to Visit 1.

7. Documented treatment with ICS and LABA for at least 3 months prior to Visit 1 with or without OCS and additional asthma controllers. The ICS and LABA can be parts of a combination product or given by separate inhalers. The ICS dose must be greater than or equal to 500 µg/day fluticasone propionate dry powder formulation or equivalent daily. For ICS/LABA combination preparations, the mid-strength approved maintenance dose in the local country will meet this ICS criterion.

   - If subjects use more than one type of ICS-containing therapy, each should be converted to fluticasone propionate equivalents and summed to derive the subject's total daily dose.

8. Additional maintenance asthma controller medications that are locally approved in a country for the treatment of asthma (eg, tiotropium, LTRAs, cromone, theophylline and oral corticosteroid), and have been used for at least 30 days prior to Visit 1, are allowed.

9. Pre-BD FEV_1 of <80% predicted (<90% predicted for patients 12 to 17 years of age) at Visit 2 (Week -3)

10. At least 2 documented asthma exacerbations in the 12 months prior to the date informed consent, and assent when applicable, is obtained that required use of a systemic corticosteroid or temporary increase from a the patient's usual maintenance dose of oral corticosteroid (please refer to Section 4.1.1). For patients who are rescreened within 30 days of their screen failure date, the calculation of the 12 month period should be done from the original informed consent date

11. ACQ-6 score ≥1.5 at Visit 1 (Week - 4)

12. Documented post-bronchodilator (post-BD) reversibility in FEV_1 of ≥12% and ≥200 mL in FEV_1 within 12 months prior to Visit 1. If historical documentation is not available, reversibility must be demonstrated and documented at Visit 2

Inclusion criteria at randomization

13. For WOCBP only: have a negative urine pregnancy test prior to administration of the IP at Visit 4

14. Fulfilment of at least one of the following conditions over the 7 days prior to randomization:

    - >2 days with a daytime or night time symptoms score ≥1
    - Rescue SABA use on >2 days
    - ≥1 nocturnal awakening due to asthma

15. Pre-BD FEV_1 of <80% (<90% predicted for patients 12 to 17 years of age) predicted at day of randomization visit

16. Patients demonstrate acceptable inhaler, peak flow meter, and spirometry techniques during run-in (from Visit 2 to Visit 4)

17. At least 70% compliance with usual asthma controller ICS-LABA during run-in period (from Visit 2 to Visit 4) based on Asthma Daily Diary. Patients who experience an asthma exacerbation during run-in may temporarily be unable to complete their diary due to illness or hospitalization. In these cases, ICS-LABA compliance will be calculated for the period after systemic corticosteroid therapy is complete.

18. Minimum 80% compliance with ePRO completion

    - 80% compliance defined as completing Asthma Daily Diary for any 8 mornings and any 8 evenings of the last 10 days of the run-in period

3.2 Exclusion criteria

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

1. Clinically important pulmonary disease other than asthma (eg, active lung infection, COPD, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome)

2. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:

   – Affect the safety of the patient throughout the study

   – Influence the findings of the studies or their interpretations

   – Impede the patient's ability to complete the entire duration of study

3. Known history of allergy or reaction to the IP formulation

4. History of anaphylaxis to any biologic therapy

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

6. Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent, and assent when applicable, is obtained or during the screening/run-in period

7. Any clinically significant abnormal findings in physical examination, vital signs, haematology, clinical chemistry, or urinalysis during screening/run-in period, which in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to complete entire duration of the study

8. Any clinically significant cardiac disease or any ECG abnormality obtained during the screening/run-in period, which in the opinion of the Investigator may put the patient at risk or interfere with study assessments

9. History of alcohol or drug abuse within 12 months prior to the date informed consent, and assent when applicable, is obtained

10. Positive hepatitis B surface antigen, or hepatitis C virus antibody serology, or a positive medical history for hepatitis B or C. Patients with a history of hepatitis B vaccination without history of hepatitis B are allowed to enrol

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

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

13. History of cancer:

    – Patients who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent, and assent when applicable, was obtained

    – Patients who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to the date informed consent, and assent when applicable, was obtained

14. Use of immunosuppressive medication (including but not limited to: methotrexate, troleandomycin, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid, or any experimental anti-inflammatory therapy) within 3 months prior to the date informed consent, and assent when applicable, is obtained. Chronic maintenance prednisone for the treatment of asthma is allowed.

15. Clinically significant asthma exacerbation, in the opinion of the Investigator, including those requiring use of OCS, or an increase in maintenance dose of oral corticosteroids 14 days prior to the date of informed consent, and assent when applicable.

16. Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent, and assent when applicable, is obtained

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

18. Receipt of live attenuated vaccines 30 days prior to the date of randomization; the exception being that for adolescent patients from the EU, receipt of live attenuated vaccines must not be within 4 months or 5 half lives prior to the date of informed consent, and assent when applicable, whichever is longer

    – Receipt of inactive/killed vaccinations (eg, inactive influenza) are allowed provided they are not administered within 1 week before/after any IP administration

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

20. Previously randomized in any benralizumab (MEDI-563) study

21. Initiation of new allergen immunotherapy is not allowed within 30 days prior to the date of informed consent, and assent when applicable. However allergen immunotherapy initiated prior to this period can be continued provided there is a gap of 7 days between the immunotherapy and IP administration.

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

23. Planned surgical procedures during the conduct of the study

24. Currently breastfeeding or lactating women

25. Previous randomization in the present study

26. Concurrent enrolment in another clinical trial

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

28. Employees of the study centre or any other individuals involved with the conduct of the study, or immediate family members of such individuals

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

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

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

3.3 Patient enrolment and randomization

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

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

The Investigator will:

1. Obtain signed informed consent, and assent when applicable, from the potential patient before any study specific procedures are performed.

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 unique randomization code via IWRS/IVRS.

Adult patients and adolescent patients in RoW non-EU countries will be allocated to 3 treatment arms in a 1:1:1 ratio (see Figure 1). Adolescent patients in EU will be allocated to 2 treatment arms described previously in the protocol in a 1:1 ratio (see Figure 2). The randomization will be stratified by ICS dose at Visit 1 (high/medium), country (for adults)/region (for adolescents) and by eosinophil count (local laboratory) at Visit 1 (≥300/μL or <300/μL) and the randomization numbers will be grouped in blocks. When a stratum is full, patients who fall within that stratum will not be randomized and will be screen failed from the study (see Section 3.7.2).

Specific information concerning the use of the IWRS/IVRS will be provided in the separate manual. Randomized patients who discontinue from the IP administration will not be replaced.

3.4 Procedures for handling incorrectly enrolled or randomized patients

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

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

3.5 Concomitant medications, restrictions during and after the study

3.5.1 Concomitant medication

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

Note: to satisfy inclusion criterion 7 the history of continuous treatment with ICS-LABA at the protocol designated doses for at least 3 months prior to Visit 1 should be documented in source and recorded in the eCRF (see Section 4.1.1).

3.5.1.1 Background medication

All patients are required to be treated with ICS and LABA for at least 3 months prior to Visit 1 and during the course of the study.

The aim of this study is to establish the treatment effect of benralizumab as add-on therapy. Therefore the background asthma controller medications should be maintained at a stable dose from Visit 1 until the end of the study. If changing the ICS-LABA dose is judged as necessary by the Investigator, the justification should be documented in the source and the change in the doses should be reflected in the eCRF.

Background medication is not regarded as an IP, but will be provided by AstraZeneca according to local regulations, in order to maintain appropriate oversight and access to this concomitant therapy.

Additional controllers that are labeled for asthma and allowed per protocol (see 3.1, criterion 8) will be provided by AstraZeneca.

3.5.1.2 Rescue medication

Salbutamol, or 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 nebulised short-acting β_2 agonists (SABA) as rescue medication can continue their use throughout the study.

As with background ICS-LABA medication, rescue medication is not regarded as an IP, but will be provided by AstraZeneca according to local regulations, in order to ensure access to essential rescue therapy.

3.5.2 Restrictions

3.5.2.1 Asthma medication restrictions

(a) Use of short-acting β_2 agonists (SABA)

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

Prophylactic use of SABA in the absence of symptoms (eg, prior to planned exercise) is discouraged. However, if deemed necessary by the patient and Investigator, it can be used, but prophylactic inhalations should not be recorded in the Asthma Daily Diary. Such use should be documented in medical notes and recorded in the eCRF.

SABA via a metered dose device is permitted as needed for worsening asthma symptoms (ie, rescue use) and will be recorded in the Asthma Daily Diary as number of inhalations.

Rescue use of SABA administered via jet or ultrasonic nebulisation is allowed. Occasions where SABA was administered via nebulisation will be recorded separately from metered dose inhaler (MDI) inhalations in the Asthma Daily Diary.

(b) **Use of short acting anticholinergics** (eg, ipratropium) as a rescue treatment for worsening asthma symptoms outside of managing an asthma exacerbation event is not allowed from enrolment and throughout the study duration

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

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

The patient's usual pre-study ICS-LABA formulation, dose and regimen, and any other additional allowed asthma controllers that they may have been taking prior to enrollment, should be continued unchanged throughout the run-in and treatment period. Additional maintenance asthma controller medications that are locally approved in a country for the treatment of asthma (eg, tiotropium, LTRAs, cromone, theophylline, and OCS), that have been used for at least 30 days prior to Visit 1, are allowed.

Patients on theophylline should have blood concentration levels checked, assessed and documented prior to randomisation. The theophylline level must not exceed the upper limit of the therapeutic range.

Changes to the patient's background controller regimen are discouraged during the treatment period, unless judged medically necessary by the Investigator; ideally such changes should be discussed with the AstraZeneca Study Team Physician. All changes in the patient's background medication should be documented in source along with rational for change and recorded in eCRF. Asthma exacerbations should be treated with oral or other systemic corticosteroids according to standard practice.

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

Pre- and/or post-BD spirometry assessments will be performed at the study centre at scheduled visits (see Table 1 and Table 2): restrictions to patient's background medication are required prior to the spirometry as described below (also see Section 5.1.2):

Screening Visit 2: Patients should withhold their usual ICS-LABA medications on the morning of the screening FEV_1 measurement and reversibility test. 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 for eligibility assessment (see Section 3.1, inclusion criteria 9 and 12).

In case the patient does not meet the reversibility eligibility criterion or FEV_1 (<80% or <90%) eligibility criterion, and a second re-test is done (not earlier than next calendar day and not later than 7 calendar days after the failed attempt), asthma medication restrictions described above should be applied.. In addition, SABA should not be used within 6 hours of these spirometry assessments. The patient's usual asthma medications may be administered following completion of the screening lung function procedures.

Treatment Visits 4-19: Patients should withhold their usual ICS-LABA medications on the morning of the scheduled spirometry. 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 prior to the spirometry assessment. This is especially important prior to scheduled spirometry assessments (see Table 2) in order to maintain the integrity of planned efficacy analyses around lung function improvement. In addition, SABA should not be used within 6 hours prior to the spirometry assessments. The patient's usual asthma controller medications may be administered following completion of the pre-BD spirograms. The suggested order of administration of the patient's usual asthma controller, per protocol SABA (on visits where post-BD spirometry is assessed), and IP administration relative to scheduled pre and post-BD spirometry is given in Section 5.1.2.

If the patient has taken their usual ICS-LABA, or LAMA 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 centre visit spirometry they should ideally remain at the centre until such time that the 6 hour withholding time has been reached if it does not exceed the 1.5 hour spirometry window, or return on another day, within the visit window.

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

Patients should avoid taking their morning asthma controllers prior to the morning Home Peak Expiratory Flow (PEF) testing, and should conduct the evening home PEF testing before taking evening asthma controllers. When possible, home PEF testing, should be taken at least 6 hours after the last dose of SABA rescue medication.

(g) 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.

(h) Asthma medication restrictions at centre visits with scheduled ECG assessment

The patients should be instructed not to take their usual asthma controller medication (ie, LABA) prior to scheduled ECG assessment. Use of SABA should be avoided within 6 hours before ECG assessments. The medication restriction is waived for the screening ECG and Visit 1.

3.5.2.2 Other medication restrictions

(a) Use of immunosuppressive medication (other than prior, stable OCS for the maintenance treatment of asthma) or administration of live/attenuated vaccines is not allowed. Topical administration of immunosuppressive medication may be allowed at the discretion of the Investigator after discussion with the AstraZeneca Study Physician. Please see Section 3.2 exclusion criteria 14 and 18 for examples and further details.

(b) Receipt of live attenuated vaccines within 30 days prior to randomization, during the treatment period, and for 16 weeks (5 half-lives) after the last dose of the investigational product is not allowed

- For adolescent patients from EU: within 4 months or within 5 half lives prior to the date informed consent, and assent when applicable, is obtained, whichever is longer

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

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

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

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

3.5.2.3 Other restrictions

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

(b) Patients must abstain from donating blood, plasma from the time of informed consent, and assent when applicable, 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 infestations 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

   (d) An asthma-related event requiring mechanical ventilation.

[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; one unsuccessful effort to check the vital status of the patient using publicly available sources, if allowed by local regulations.

All patients who prematurely discontinue IP should return to the study centre and complete the procedures described for the Premature IP Discontinuation Visit (IPD) within 4 weeks (+7 days).

At that visit, patients should be encouraged to remain in the study to complete all subsequent study visits, procedures and assessments or alternatively agree to be contacted by phone calls at monthly intervals in order to collect AEs/Serious Adverse Events (SAEs), changes in concomitant medication, health care utilisation, and asthma exacerbation information. Patients not willing to continue to participate in the study should return to the study centre one last time at 8 weeks (±7 days) after the last dose of IP for final study related assessments.

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

3.7 Withdrawal from the study

3.7.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomized. These patients should have the reason for study withdrawal recorded in eCRF.

3.7.2 Withdrawal due to recruitment completion in a randomization stratum

When a specific stratum is full, patients in completed stratum will not be randomized and will be withdrawn from the study. The reason of the withdrawal should be documented in the source and eCRF as a development of study specific criteria for discontinuation. As with screen failures, no further study related follow-up of these patients is required.

Strata closure process:

1. The high-dose-ICS with eosinophil <300/μL stratum will be closed to adult patients when the total number of adult and adolescent patients in the stratum reaches approximately 342

2. The medium-dose-ICS with eosinophil ≥300/μL stratum will be closed to adult patients when the total number of adult and adolescent patients in the stratum reaches approximately 180

3. The medium-dose-ICS with eosinophil <300/μL stratum will be closed to adult patients when the total number of adult and adolescent patients in the stratum reaches approximately 90.

4. The adolescents stratum with eosinophil <300/μL stratum will be closed when the total number of adolescent patients in
altogether in the <300/μL stratum reaches approximately 70.

5. The whole study will be closed for recruitment when the total number of adult and adolescent patients in the high-dose-ICS with eosinophil ≥300/μL stratum reaches approximately 684.

3.7.3 Withdrawal of the Informed Consent

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

A patient who withdraws consent, and assent when applicable, will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up AEs outside of the clinical study. The patient will return electronic PRO (ePRO) devices. The enrolment/randomization code of the withdrawn patient cannot be reused.

If patient agrees, he/she will be asked to return to the study centre and complete procedures described for the IPD and Follow up visits within 4 weeks (+7 days) and 8 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, and assent when applicable, to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, 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, and assent when applicable, for the retention of samples for future exploratory use (eg, study of markers of asthma, identifying potential new drug targets for asthma, or for assay development purposes), patient will not be withdrawn from the study.

The Principal Investigator or designee:

- Ensures patients' withdrawal of informed consent, and assent when applicable, for the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study centre, 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, and assent when applicable, 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, and assent when applicable, immediately and that samples are disposed of/destroyed and the action documented and returned to the study centre.

4. STUDY PLAN AND PROCEDURES

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

Assessment/ activity	**Refer to**	**Enrolment**	**Screening/ run-in**	
		V1 (W –4)	**V2[a] (W –3)**	**V3[f] (≤W –1)**
		Visit window (days)		
		14 – 35 days[e]		
Informed consent	10.4	X		
Inclusion/exclusion criteria	3.1/3.2	X	X	X
Medical and asthma history	4.1.1	X		
Complete physical examination	5.2.1.1	X		
Weight, Height	5.3.1	X		
Vital Signs	5.2.2	X		X
Local ECG	5.2.3	X		X
Local laboratory eosinophil test	5.3.5.1	X		
Blood concentration for drugs with narrow therapeutic range [d]	5.2.4	X		
Serum chemistry	5.2.4	X		X
Haematology	5.2.4	X		X
Urinalysis	5.2.4	X		X
Serology (hepatitis B,C; HIV-1; HIV-2)	5.3.5.2	X		

Assessment/ activity	Refer to	Enrolment	Screening/ run-in	
		V1 (W –4)	V2[a] (W –3)	V3[f] (≤W –1)
		Visit window (days)		
		14 – 35 days[e]		
Serum pregnancy test[g]	5.2.4.1	X		
FSH [b]	5.2.4.1	X		
Screening reversibility [c]	5.1.2.1		X	
Home PEF Testing	5.1.3		X	X
Asthma Daily Diary adherence	5.3.2.1		X	X
ACQ-6 adherence	5.3.2.2	X	X	X
Health care resource	5.3.3	X		
Pre- BD, spirometry	5.1.2		X	
Adverse events	7.1	X	X	X
Concomitant medication	3.5	X	X	X

[a] Visit 2 may take place as soon as medication restrictions prior to spirometry/reversibility tests at this visit are met (see Section 3.5.2), and should occur no later than 1 week after Visit 1

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

[c] When historical proof of post-BDreversibility in FEV_1 is documented within 12 months prior to Visit 1, the screening reversibility does not need to be performed, otherwise the test to be done on Visit 2. For details please refer to Section 4.1.2

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

[e] Not applicable for patients with exacerbation during screening period (see Section 4.1.3.1)

[f] Visit 3 and Visit 4 may take place the same day.

[g] Serum beta-HCG: To be done in all females at screening Visit 1 except for those who are NOT of child bearing potential as defined in inclusion criterion 3.

D Days; EOT End-of-treatment; FU Follow-up; R Randomization; V Visit; UNS Unscheduled; W Week.

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

Assessment/ activity	Refer to	R	Treatment														EOT	IPD	FU [f]	UNSh
		V4	V5 phone	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19		V20	
		W0	W0d6	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56		W60	
		Visit window (days) [a]																		
		±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																		
Complete physical examination	5.2.1.1	X															X	X		X
Brief physical examination	5.2.1.2			X	X	X	X	X	X	X	X	X	X	X	X	X				
Weight	5.3.1	X							X								X	X		
Height	5.3.1																X	X		
Vital Signs	5.2.2	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Local ECG	5.2.3								X								X	X		
Serum chemistry [b]	5.2.4			X	X				X				X				X	X		
Haematology	5.2.4			X	X				X				X				X	X	X [c]	
Urinalysis	5.2.4			X	X				X				X				X	X		
Urine pregnancy test (dipstick) [d]	5.2.4.1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
TBNK Flow Cytometry	5.3.6	X			X				X				X				X	X	X	
Immunoglobulins (Total IgG, IgA,	5.3.5.3	X			X				X				X				X	X	X	

Assessment/ activity	Refer to	R	Treatment														EOT	IPD	FU [f]	UNSh
		V4	V5 phone	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19		V20	
		W0	W0d6	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56		W60	
		Visit window (days) [a]																		
		±0	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	±7	N/A
IgM and IgE)																				
Phadiatop	5.3.5.4	X																		
PK	5.3.7	X		X	X		X		X		X		X		X		X	X	X	
ADA/nAb [e]	5.3.9	X			X		X		X		X		X		X		X	X	X	
Serum biomarkers	5.3.8.1	X		X					X								X	X	X	
Home PEF adherence	5.1.3	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Asthma Daily Diary adherence	5.3.2.1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ACQ-6 adherence	5.3.2.2	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AQLQ(S)+12 adherence	5.3.2.3	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
WPAI+CIQ adherence	5.3.2.4	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
EQ-5D-5L adherence	5.3.2.5	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CGIC and PGIC	5.3.3						X		X		X						X			
Health care resource utilization	5.3.4			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Assessment/ activity	Refer to	R	Treatment														EOT	IPD	FU [f]	UNSh
		V4	V5 phone	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19		V20	
		W0	W0d6	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56		W60	
		Visit window (days) [a]																		
		±0	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	±7	N/A
Assessment of asthma exacerbations	5.1.1	X		X	X	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		X		X		X		X	X		X
Post- BD spirometry	5.1.2	X							X								X	X		
Randomization	4.2/6.5	X																		
Administration of IP for adults and adolescents in RoW[g]	6.8	X		X	X	X	X	X	X	X	X	X	X	X	X	X				
Administration of IP for adolescents in EU[g]	6.8	X		X	X		X		X		X		X		X					
Adverse events	7.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	3.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] All visits are to be scheduled from the date of randomization but not from the date of previous visit
[b] Detailed schedule for serum chemistry tests provided in Section 5.2.4, Table 3
[c] Eosinophil count to be measured only
[d] For all females except those NOT of child bearing potential as defined in inclusion criterion 3, urine HCG test to be done at centre on each treatment visit before IP administration

[e] All ADA positive samples with the exception of those from Week 8 will be tested for neutralizing antibodies (nAb)

[f] Patients that complete the double blind treatment period on IP may be enrolled into a follow-on extension study and will not attend the Follow-up visit. Patients who complete the treatment on IP and do not enter the extension study at the EOT visit will return at Week 60 for a final Follow-up visit

[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

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

4.1 Enrollment and screening/run-in period

4.1.1 Enrollment (Visit 1)

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

Patient must sign the ICF prior to any Visit 1 procedures. Those procedures must be initiated within 3 working days from the date of ICF. Registration of patient's enrollment via IWRS/IVRS should occur on day when other Visit 1 procedures are done.

Visit 1 assessments are primarily concerned with confirmation of the asthma disease state, the requisite level of severity based on background medications and exacerbation history, and the current level of control based on an initial ACQ-6 score.

A record of physician-diagnosed asthma, ICS-LABA use (Section 3.1, criteria 6 and 7) and asthma exacerbations over the prior year (Section 3.1, criterion 10) is required source documentation. A patient verbal history suggestive of asthma symptoms and/or prior asthma exacerbations, but without supporting documentation, is not sufficient to satisfy these inclusion criteria.

Examples of acceptable documentation of the asthma disease state and prior asthma exacerbations include clinic visit (primary or specialist HCP), emergency room/urgent care, or hospital records listing asthma as a current problem, plus documentation of at least 2 asthma exacerbations during the 12 months prior to ICF:

> A qualifying historical asthma exacerbation is a symptomatic worsening requiring systemic corticosteroid (ie, oral, intravenous or intramuscular; any healthcare setting) or temporary increase from a stable maintenance dose of OCS, or that resulted in hospitalization.

Current, regular use of an ICS and LABA for at least 3 months prior to enrolment must be documented in the source. This may have been administered as either as fixed dose or 2 or more separate inhalers, and consistent with dose limits set by inclusion criterion 7. This documentation may be in the form of a recent, active medication list as per an HCP note, or filled prescriptions based on a pharmacy record.

Patients will continue on their current asthma treatment with no changes.

4.1.2 Screening/run-in (Visit 2, Visit 3)

The run-in period should be a minimum of 2 weeks in duration (from Visit 2 to Visit 4). The patient should remain on their current asthma treatment with no changes throughout screening/run-in period. Assessments applicable for the period are listed in Table 1.

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

Visit 2 may be performed as a telephone visit if the patient is confirmed as ineligible for the study (eg, based on laboratory results from Visit 1 or medical history).

Visit 2 may take place as soon as medication restrictions prior to spirometry/reversibility tests are met (see Section 3.5.2), and should occur no later than 1 week after Visit 1. Visit 2 procedures may be performed on the same day as Visit 1 if the medication restriction is met. If Visit 2 procedures are actually planned at Visit 1 as a convenience, then the ICF must be signed prior to Visit 1 and prior to instructing the patient to withhold any medication.

If a patient fails the protocol-specified reversibility criterion (12% FEV_1 and 200 ml) or FEV_1 (<80% or <90%) criterion, a second attempt is allowed. Re-testing can only occur once during the run-in period, not earlier than next calendar day and not later than 7 calendar days after the failed attempt.

Note: In cases when historical proof of post-BD reversibility in FEV_1 (see inclusion criterion 12) is documented within 12 months prior to Visit 1 the screening reversibility does not need to be performed (see Section 5.1.2.1).

Once the reversibility criterion has been met, the patient will be supplied with an electronic hand-held spirometer (peak flow meter) to monitor home lung function, and an ePRO device to record asthma symptoms and complete relevant questionnaires (see Section 5.3.2 for further details).

Visit 3 can be performed within 1 week before Visit 4 or on the same day as Visit 4. If visit 3 and Visit 4 are combined then all procedures from both visits should be done.

On Visit 3 ACQ-6 will be recorded (for baseline purposes only). Patient's eligibility should be evaluated at each visit during the screening/run-in period with the relevant documentation entered in the source and eCRF

4.1.3 Re-screening

Re-screening is allowed only once for the patient.

Patients who experience an asthma exacerbation during the screening/run-in period may remain in screening and may proceed with study visits after they have completed their course of systemic steroids or returned to their maintenance dose of OCS.

Patients with respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent, and assent when applicable, is obtained or during the screening/run-in period may also be re-screened.

If the reason for screen failure was transient (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits), patients may potentially be re-screened. These cases should be discussed with the AstraZeneca Study Physician and documented in the Investigator Study File (ISF). For those patients who were screen failed at Visit 3 or thereafter re-screening period could be reduce. Visit 1 and Visit 2

can be done at the same day; Visit 3 can be done 1 week after Visit 2, and Visit 4 one week after Visit 3.

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

IMPORTANT! Re-screening for patients who have screen-failed due to an ACQ score <1.5 is not allowed.

4.1.3.1 Procedures for patients who experience an exacerbation during screening

Patients who experience an asthma exacerbation between Visit 1 and Visit 4 should be treated according to local medical practice and may continue screening at the discretion of the Primary Investigator. More than one exacerbation during screening will result in screen-failure.

- **Exacerbations between Visit 1 and Visit 3**:
  - The next regular study visit (Visit 2 or Visit 3) will be delayed and may proceed no sooner than 14 days after the last dose of systemic steroids.
  - For patients on chronic OCS therapy, Visit 2 or Visit 3 can commence minimally 14 days after the daily dose has returned to the pre-exacerbation baseline level.
  - A local eosinophil count should not be repeated.
- **Exacerbations between Visit 3 and Visit 4**:
  - Visit 4 will be delayed. Patients will return to the centre for an unscheduled visit at the time their systemic steroid regimen is complete or the dose of OCS has returned to baseline.
  - Central laboratory safety assessments will be collected (see Table 3) at the unscheduled visit and checked by the Investigator prior to randomization.
  - A local eosinophil count should not be repeated. Patients will be assigned to an eosinophil stratum (≥300/μL or <300/μL) based upon the Visit 1 local eosinophil count that was obtained prior to the exacerbation.
  - Randomization at Visit 4 can commence minimally 14 days after the systemic steroid regimen is complete or the dose of OCS has returned to baseline.
- **Exacerbations at Visit 4**:
  - Patients who are diagnosed with an asthma exacerbation at Visit 4 should be screen-failed.

Electronic diary assessments should be completed during the delay between study visits.

Patients who are screen-failed with an exacerbation at Visit 4 or due to exacerbation between Visit 1 and Visit 4 may be re-screened one time.

4.2 Randomized treatment period

Inclusion criteria at randomization will be confirmed at Visit 4. Before randomization the patient's compliance with usual asthma controller ICS-LABA and ePRO completion must be confirmed (see Section 3.1, inclusion criteria 17 and 18).

Patients confirmed to be eligible will be randomized at Visit 4 (Week 0).

Adults, adolescents in RoW and adolescents in EU will be randomized to one of the treatment arms as described in Section 1.5 and shown on Figure 1 and Figure 2.

The first dose of the IP will be administered at Visit 4 after the patient's randomization via IWRS/IVRS.

During Visit 4, but before the first dose of IP, the patient should complete the following PRO assessments on the ePRO device: AQLQ(S)+12, ACQ-06, WPAI+CIQ, and EQ-5D-5L.

For Visits 6 -18, spirometry and blood sampling (for hematology, serum chemistry, PK, ADA/nAb, and when applicable, serum biomarkers) may be performed one day prior to the scheduled date of IP injection, at the discretion of the Investigator. All other study procedures must be done on the scheduled day of IP injection. Urine pregnancy tests must be done on injection days, prior to IP administration. Following randomization the patient will receive 56-week double-blind treatment, with the last dose of benralizumab/placebo administered at Visit 18 (Week 52).

Patients will have scheduled visits at 4-week interval to complete protocol-specific assessments and IP administration, as listed in Table 2; Restrictions as set out in Section 3.5.2 will continue to apply throughout the treatment period. In case of an asthma worsening/exacerbation (see Section 5.1.1), patients should be evaluated at the study centre, when feasible, at an unscheduled visit, or ordinary visit if the worsening happens to fall within a scheduled visit window.

Patients will continue to monitor lung function at home, as well as record asthma symptoms and responses to questionnaires using ePRO device throughout the 56-week treatment period (see Section 5.3.2 for details).

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

Patients who prematurely discontinued IP (see Section 3.6) and are not willing to continue to participation in the study should return to the study centre and complete procedures described for the EOT and Follow up visits within 4 weeks (+7 days) and 8 weeks (±7 days) after the last dose of IP, respectively.

Patients will return the ePRO device on EOT visit.

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

4.3 Follow-up period

Patients that complete the double blind treatment on IP may be enrolled into a follow-on extension study.

Those patients who complete the treatment on IP and do not enter the extension study at the EOT visit (Week 56) will return at Week 60 for a final Follow-up visit.

5. STUDY ASSESSMENTS AND PROCEDURES

5.1 Efficacy assessments

5.1.1 Assessment of asthma exacerbations

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

- Use of systemic corticosteroids (or a temporary increase in a stable OCS background dose) for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids
- An emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as per above)
- An inpatient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma

Worsening of asthma is defined as new or increased symptoms and/or signs (examination or lung function) that can be either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (diary-driven). The ePRO device will be programmed to alert both the patient and study centre when certain pre-specified worsening thresholds are crossed including:

- Decrease in morning peak flow ≥30% on at least 2 of 3 successive days compared with baseline (last 10 days of run-in), and/or
- A ≥50% increase in rescue medication or one new or additional nebulized β2 agonist on at least 2 of 3 successive days compared with the average use for the previous week, and/or
- Nocturnal awakening due to asthma requiring rescue medication use for at least 2 of 3 successive nights, and/or
- An increase in total asthma symptom score (the sum of day time [evening assessment] and night time [morning assessment] of at least 2 units above the run-in average (last 10 days of run-in), or the highest possible score (daily score of 6), on at least 2 of 3 successive days

If an exacerbation event is not associated with deterioration in at least 1 of the pre-specified objective measurements, the Investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF. Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

An asthma exacerbation that occurs ≤7 days of 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.

Reasonable attempts should be made by the Investigator to bring the patient into the study centre for evaluation of a diary alert or patient initiated asthma worsening, particularly when it results in additional treatment being prescribed. Study centre evaluations for asthma worsening may occur as an unscheduled visit or as part of an ordinary centre 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 centres (eg, by the primary care HCP or at an emergency department/hospital) and details entered into the exacerbation eCRF (EXACA) 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 centre will be measured by spirometry using equipment provided by central vendor. Spirometry will be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.(Miller et al 2005).

The central spirometry vendor is responsible for assuring that the spirometer meets ATS/ERS recommendations and that the study centre personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate spirometry procedures manual.

Important! Asthma medication restrictions described in Section 3.5.2 should be followed and the spirometry assessment should be performed when those restrictions are met. Options for handling patients who have inadvertently taken their asthma medication within the restricted window are described in Section 3.5.2.

Time of day for scheduled centre visit spirometry

Spirometry testing should be done according to the schedule provided in Table 1 and Table 2. All post-randomization spirometry assessments should be performed within ± 1.5 hours of the time that the randomization spirometry was performed. For example, if the randomization spirometry was started at 8:00 AM, then all subsequent spirometry testing needs to be initiated between 6:30 AM and 9:30 AM.

Spirometry technique

Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Patients should avoid eating a large meal for at least 2 hours prior to spirometry measurements at the centre. Forced expiratory manoeuvres 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 manoeuvre from enrolment throughout the study. The head must not be tilted during manoeuvres and the thorax should be able to move freely; hence tight clothing should be loosened. A nose-clip should be used for the manoeuvre. Mouthpieces of the same dimension and shape should be used by the patient from enrolment throughout the study.

The forced expiratory manoeuvre (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 manoeuvre. 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 centre 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 to satisfy reversibility inclusion criterion 12 (for patients without prior documentation of reversibility) and as an efficacy measure on designated centre visits during the treatment period as listed in Table 2. The post-BD spirometry procedures should commence within 30±15 minutes according to the regimen for reversibility testing outlined in Section 5.1.2.1.

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

The patient's usual asthma morning asthma controller therapy must not be given until after the initial pre-medication, pre-BD spirograms are complete for the reasons discussed above; usual asthma controller may be given after final post-bronchodilator spirograms. IP dosing should also be withheld until pre-BD spirometry is complete. Given the mandatory 2-hour observation period, IP can be administered as soon as the second round of SABA is completed (ie, 4 inhalations +2 inhalations) in order to help expedite the visit. This option of administering IP between the second and third round of puffs can only be done in the absence of SABA related symptoms (tremor or effects on heart rate).

Record keeping

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

Spirometry references

The Global Lung Function Initiative (GLI) equations will be used to determine the patients predicted normal (PN) values and are pre-programmed into your spirometer (Quanjer et al 2012).

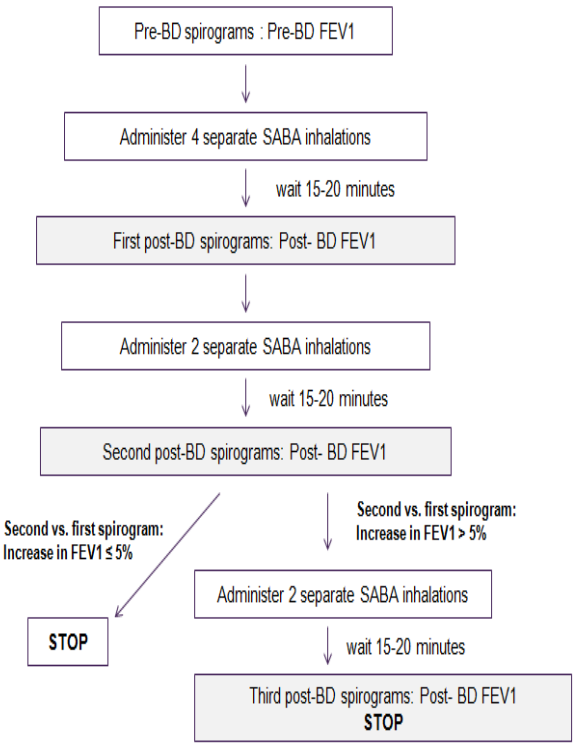
FEV_1 expressed as percent of the PN value will be calculated as follows:

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

5.1.2.1 Reversibility test and post-BD FEV1 efficacy assessment

The procedure described in this section refers both to the reversibility testing at Visit 2 (to evaluate inclusion criterion 12, if applicable) and to the post-BD FEV_1 efficacy endpoint at prespecified visits from V4 and onwards. If a reversibility maneuver that meets ATS (American Thoracic Society) criteria (12% and 200 mL) is rejected as the best maneuver after central overreading, it may still be used to satisfy Inclusion Criterion 12. Maximal bronchodilatation should be induced using albuterol (90µg metered dose), or 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. Nebulizer should not be used. The algorithm for reversibility testing is outlined in Figure 3.

Figure 3 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. **4** 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. For the visit 2 reversibility testing, it is acceptable to stop the procedure when the eligibility criterion is met. Please note that for the post-BD FEV1 efficacy assessment, the same procedure (ie, the same bronchodilator, device, number of puffs etc) should be used at all visits from Visit 4 and throughout the study.

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

% Difference=FEV_1(6 puffs)-FEV_1(4 puffs)/FEV_1(4 puffs)×100

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

Reversibility is calculated as follows:

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

Note: In cases when historical proof of post-BD (post-BD) reversibility in FEV_1 (see inclusion criterion 12) is documented within 12 months prior to Visit 1, the screening reversibility test does not need to be performed.

5.1.3 Home Peak Expiratory Flow testing

An electronic, hand-held spirometer (peak flow meter) will be dispensed to the patient on Visit 2 (after respiratory inclusion criteria have been confirmed, see Section 3.1, criteria 9 and 12).

Home peak expiratory flow (PEF) testing will be performed by the patient in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Recording of home lung function should start from the evening of Visit 2 (Week -3) until the morning of Visit 19 (Week 56) using an ePRO device. When possible, ambulatory lung function measurements should be taken at least 6 hours after the last dose of SABA rescue medication.

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

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

5.2 Safety assessments

5.2.1 Physical examination

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

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

5.2.1.1 Complete physical examination

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

5.2.1.2 Brief physical examination

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

5.2.2 Vital signs

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

The vital signs will be taken prior to IP administration, and, if possible, blood drawing and usual asthma controller medication. If it is not logistically possible, 10 minutes should be allotted between phlebotomy and vital signs assessment. Vital signs should also be taken prior to per protocol bronchodilator administration if applicable for that visit.

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

Respiration rate will be obtained after patient has been resting for at least 5 minutes, by counting number of breaths (how many times the chest rises) for 1 minute.

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

5.2.3 ECG

ECG will be performed in accordance with schedule provided in Table 1 and Table 2. The assessment will be done in supine position, after the patient has been resting for at least 5 minutes.

A standard 12-lead ECG with a recommended paper speed of 50 mm/second covering at least 6 sequential beats will be used. The Investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. In case of discrepancy between the Investigators interpretation and that provided by the ECG machine (if applicable), the Investigators interpretation 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. In all patients, the printouts of the ECG will be collected, signed, dated and stored at the study centre along with a signed and dated copy (if the printouts are not on archive-quality paper).

5.2.4 Safety laboratory tests

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

Haematology and urinalysis will be assessed in line with the schedules provided in the Table 1and Table 2;a detailed schedule of the chemistry tests is presented in Table 4.

Laboratory results should be reviewed by the Investigator/authorized delegate and evaluated for abnormalities. Any laboratory abnormalities considered to be significant in the Investigators'/authorized delegate's judgement should be reported as described in Section 7.1.3.

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

Table 3 List of safety laboratory tests

Serum chemistry		Haematology	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, except Visit 1 laboratory report (see Section 6.6).

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

Table 4 Serum chemistry tests schedule

VISIT	V1	V3	V6	V7	V11	V15	V19	IPD
Alkaline phosphatise	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
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

5.2.4.1 Pregnancy Test

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

- FSH: To be done at screening Visit 1 only, for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 month
- Serum beta-HCG: To be done in all females at screening Visit 1 except for those who are NOT of child bearing potential as defined in inclusion criterion 3. This test is to be sent to and analyzed at the central laboratory.
- Urine HCG: To be performed at the study centre for all females at each treatment visit before IP administration using a dipstick except for those females who are NOT of child bearing potential as defined in inclusion criterion 3. A positive urine test result must be confirmed with serum beta HCG.

5.3 Other assessments and procedures

5.3.1 Weight and height

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

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

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

5.3.2 Patient reported outcomes

Patients will be supplied with an ePRO device and hand-held spirometer at Visit 2 after respiratory criteria have been confirmed (see Section 3.1, criteria 9 and 12). The study centre staff will be trained on how to use both devices and will be responsible for instructing patients on how to use both devices. Patients will have an opportunity to practice using the devices through a pre-programmed training module. Patients should be informed that the recordings made electronically cannot be retrospectively or prospectively entered and must be completed within a defined time window. Patients will also be provided with information about when and where to request help if problems occur.

5.3.2.1 Asthma daily diary

The Asthma Daily Diary will be completed each day from the evening of Visit 2 to the morning of Visit 19. The Asthma Daily Diary will include the following daily recordings: morning and evening home lung function data (obtained from the home peak flow meter), asthma symptoms, inhalations of rescue medication, nights with awakenings due to asthma symptoms, background medication compliance. There will be triggers in the ePRO device to alert the patients to signs of worsening of asthma and to contact their physician, please refer to Section 5.1.1.

The patient should contact the study physician for evaluation in the setting of a diary alert.

Investigator/authorized delegate will check patient's adherence to the Asthma Daily Diary at each visit as shown in Table 1 and Table 2.

Home peak expiratory flow measurement

For details regarding home lung function measurement please refer to Section 5.1.3.

Asthma symptoms

Asthma symptoms during night time and daytime will be recorded by the patient each morning and evening in the Asthma Daily Diary, from Visit 2 to Visit 19.

Daytime is defined as the time period between the morning peak expiratory flow assessment (upon rising in the morning) and the evening peak expiratory flow assessment. Night time is defined as the time period between the evening peak expiratory flow assessment (at bedtime) and the morning peak expiratory flow assessment.

Rescue medication

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

Nocturnal awakenings

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

Background medication

Background medication administration use will be recorded in the Asthma Daily Diary in the morning and evening as "yes" or "no" response.

5.3.2.2 Asthma Control Questionnaire (ACQ-6)

The ACQ-6 is a shortened version of the ACQ that assesses asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and short-acting 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 using the ePRO device.

Visit 1 ACQ-6 scores will determine eligibility for run-in and randomization, (see section 3.1, inclusion criterion 11). An initial screening the ACQ-6 will be taken at Visit 1 at study centre. Between Visit 2 and Visit 3 patients will complete the ACQ-6 on a weekly basis (±1 day). The patient will bring the device to the randomization visit and complete the ACQ-6 on site during the randomization visit (Week 0). Once randomized, patients will be asked to complete the ACQ-6 once every 2 weeks (±1 day) throughout the treatment period.

The Investigator/authorized delegate will check patient's adherence to the ACQ-6 at each visit as shown in Table 1 and Table 2.

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

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

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

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

The questionnaire will be completed using the ePRO device.

The AQLQ(S)+12 will be first completed at Visit 4 (Week 0). The patient will bring the device to the randomization visit and complete the AQLQ(s)+12 on site during the randomization visit (Week 0).

Following Visit 4 the questionnaire will be completed by the patient every 4 weeks (±1 day) at home throughout the 56-week treatment period.

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

5.3.2.4 Work Productivity and Activity Impairment questionnaire plus Classroom Impairment Questions (WPAI+CIQ)

The WPAI+CIQ consists of questions about how asthma and asthma-related issues impact the ability to work, attend classes, and perform regular daily activities. The questionnaire relates to the previous 7 days. The WPAI+CIQ will be used to measure self-reported productivity loss. The questionnaire will be completed using the ePRO device

The WPAI+CIQ will be first completed at Visit 4 (Week 0). The patient will bring the device to the randomization visit and complete the WPAI+CIQ on site during the randomization visit (Week 0). Following Visit 4, the questionnaire will be completed by the patient every 2 weeks (±1 day) at home throughout the 56- week treatment period.

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

5.3.2.5 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 weekly (±1 day) starting from Visit 4 (Week 0) throughout Week 56 (Visit 19) using the ePRO device. The patient will bring the device to the randomization visit and complete the EQ-5D-5L on site during the randomization visit (Week 0).

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

5.3.3 CGIC and PGIC assessments

Clinician Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC) instruments are used for an overall evaluation of response to treatment, conducted separately by the Investigator and the patient using a 7-point rating scale: 1 = Very Much Improved; 2 = Much Improved; 3 = Minimally Improved; 4 = No Change; 5 = Minimally Worse; 6 = Much Worse; and 7 = Very Much Worse.

The Investigator (clinician) and the patient will be asked to rate the degree of change in the overall asthma status compared to the start of treatment, ie, randomization visit. The CGIC and PGIC will be completed at site visits according to study schedule provided in Table 2. It is recommended that the same clinician completes the CGIC for an individual patient. When possible, the PCIG should be completed by the patient before other study assessments and IP administration.

5.3.4 Health care resource utilization

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

At Visit 1 (Week -4) Healthcare Resource Utilization (HRU) information will be collected with a one year recall period. The subsequent visits will collect HRU information with a recall period of 'since last visit'.

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

5.3.5 Other screening/run-in assessments

5.3.5.1 Local laboratory eosinophil test

Patients will be randomized by absolute blood eosinophil counts as assessed by a local laboratory, with the aim of randomizing patients with ≥300/µL versus those with <300/µL in a ratio of 2:1.

The expectation is that there should be **no more than 36 hours between the documented time of blood draw and the local analysis of the sample.** If this window is exceeded, the test must be repeated prior to administration of IP.

For patients who were randomized before implementation of CSP Amendment 1 (CSP AM1), the blood eosinophil count drawn at Visit 3 will be used to inform primary and secondary efficacy of benralizumab. For patients who were randomized after CSP AM1, the blood eosinophil count drawn at Visit 1 will be used to inform primary and secondary efficacy of benralizumab. The expectation is that there should be no more than 36 hours between the documented time of blood draw and the local analysis of the sample. If this window is exceeded, the test must be repeated prior to administration of IP.

5.3.5.2 Serology

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

HIV-1 and HIV-2 antibodies: To be done only at screening; test to be performed at central laboratory.

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

5.3.5.3 Immunoglobulins

The levels of total IgG, IgA, IgM, and IgE will be evaluated by a central laboratory. These tests will be performed at Visit 4 (Week 0), Visit 7 (Week 8), Visit 11 (Week 24), Visit 15 (Week 40), Visit 19 (Week 56), and Visit 20 (Week 60) (see Table 2).

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

5.3.5.4 Phadiatop

The test will be performed on Visit 4 (Week 0)(see Table 2). Analysis will be performed by central laboratory.

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

5.3.6 TBNK Flow Cytometry

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 on Visit 4 (Week 0), Visit 7 (Week 8), Visit 11 (Week 24), Visit 15 (Week 40), and Visit 19 (Week 56) and Visit 20 (Week 60) (see Table 2).

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

5.3.7 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 centres.

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

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

The PK samples will be retained for 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).

5.3.8 Pharmacodynamics

5.3.8.1 Serum biomarkers

Serum samples will be collected according to the schedule in Table 2 to evaluate the pharmacology of benralizumab as well as biomarkers of eosinophil recruitment, activation, and survival (e.g. periostin, IL-5, EDN, and eotaxin). Additional eosinophil, basophil - and inflammation-related biomarkers of asthma may also be assessed.

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

AstraZeneca or a designee will retain serum biomarker samples for investigation of the pharmacology of benralizumab for a maximum of 15 years following the Last Patient's Last Visit.

The results from the investigation of such samples will not be reported in the CSR but in separate reports and in scientific publications as appropriate.

5.3.9 Immunogenicity

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

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

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

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

Anti-benralizumab antibodies

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

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

Neutralizing antibodies

All ADA positive samples with the exception of those from Week 8 will be tested for neutralizing antibodies (nAb). The presence or absence of neutralizing ADA will be determined using a validated bioanalytical method.

5.3.10 Handling of biological samples

5.3.10.1 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),

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.

5.3.10.2 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 centre is to keep full traceability of collected biological samples from the patients while in storage at the study centre 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 centres and auditing of external laboratory providers.

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

6. MANAGEMENT OF INVESTIGATIONAL PRODUCTS

6.1 Identity of investigational product(s)

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

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

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 centre 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 centre 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 centre, unused study drugs and for appropriate destruction. Certificates of delivery, destruction, and/or return should be signed.

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

6.5 Methods for assigning treatment groups

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

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

6.6 Methods for ensuring blinding

The study will be conducted in double-blind, double-dummy fashion. AstraZeneca staff involved in the study, the patients, and the Investigators involved in the treatment of the patients or in their clinical evaluation will not be aware of the treatment allocation.

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

Maintaining the blind to the patient's blood eosinophil counts

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

- From Visit 4 on, monocyte counts will be redacted from central laboratory reports to prevent the Principal Investigator/designee from possibly deducing the 'eosinophil + basophil' contribution to the complete blood count.

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

- **Handling of labs obtained during the treatment period but ordered outside of the clinical trial**. Centre staff who are directly involved in the patient's management should remain blinded to any eosinophil, basophil and monocyte results included as part of outside lab reports. To help ensure this, each investigational centre 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 centre staff involved in the patient's management and prior to filing as a source document. Similarly, eosinophil and basophil results must be redacted from all communications with the Sponsor.

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

6.7 Methods for unblinding

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

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

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

6.8 IP administration and treatment compliance

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

The IP will be administered at the study centre on treatment visits and within visit windows as specified in 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 IP administration

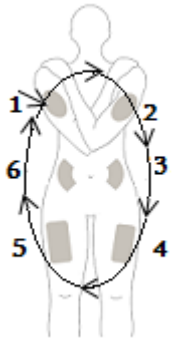
Prior to each IP administration:

- Investigator/authorized delegate will assess injection site as per standards of medical care
- For all females except for those who are NOT of WOCBP as defined in inclusion criterion 3 urine pregnancy test will be done; IP will be administered only when the result of the test is negative (see Section 5.2.4.1)

IP 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 4). The injection site should be recorded in the source documents and the eCRF at each treatment visit.

Figure 4 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 IP administration

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

Conditions requiring IP administration rescheduling

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

6.9 Management of IP-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).

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

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

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

3. Reduced blood pressure after exposure

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

In order to help understand the potential drug-relatedness of any acute reaction, a blood sample should be drawn as close as possible to 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 hospitalisation or prolongation of existing hospitalisation
- 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 jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

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, and assent when applicable, throughout the treatment period and including the follow-up period (Visit 20, week 60).

7.1.3.2 Follow-up of unresolved adverse events

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

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

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

7.1.3.3 Variables

The following variables will be collect for each AE;

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

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

7.1.3.4 Causality collection

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

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

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 summarised 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 haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

NB. Cases in which a patient shows an AST or ALT ≥3xULN or total bilirubin ≥ 2xULN may need to be reported as SAEs

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 centre 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 centre 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 h** from when he or she becomes aware of it.

Once the Investigators or other centre 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 centre personnel is to report a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study centre 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 centre 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

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 centre 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

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

8.2 Sample size estimate

The study will recruit patients with blood eosinophil counts ≥300/μL and <300/μL at a ratio of about 2:1. The 2:1 stratification ratio is intended as a means of enriching the population for patients most likely to respond to benralizumab (ie ≥300/μL), while still including patients below this threshold in order to help understand efficacy and safety in this group. The study is powered for the primary efficacy analysis of the high-dose-ICS patients with blood eosinophils ≥300/μL.

The efficacy analyses will comprise both adults and adolescent patients.

For the primary endpoint annual asthma exacerbation rate, around 228 high-dose-ICS adults and adolescent patients with baseline blood eosinophil counts ≥300/μL per treatment arm (approximately 684 total) will need to be randomized to achieve 90% power of detecting a 40% reduction in both benralizumab dose regimens versus placebo based on the testing strategy to adjust for multiplicity considerations (see Section 8.5). This calculation has assumed two-sided 4% alpha level tests and an annual placebo rate of 0.88 events/patient based on published data and The sample size calculation is based on simulations and a negative binomial shape parameter is of 0.9.

As stated previously an about 2:1 ratio will be used for patients with blood eosinophil counts ≥300/μL and <300/μL. Therefore the study will also enrol around 114 high-dose-ICS patients/arm (approximately 342 total) with baseline blood eosinophil counts <300/μL. In addition it is expected that approximately 270 medium-dose-ICS patients (around 60 patients

with eosinophil counts ≥300/μL and around 30 patients with eosinophil counts <300/μL per arm) will be recruited. So a total of around 1296 patients are expected to be randomized in the study.

The sample size necessary to achieve a stated power (90% in our case) in this study is calculated based on the estimate of overall exacerbation rate and shape parameter from the negative binomial model (Section 8.5.1). In order to better estimate the overall exacerbation rate and shape parameter, we plan to conduct a blinded sample size re-estimation. Blinded estimates of the overall exacerbation rate as well as the shape parameter from data pooled across placebo and all benralizumab doses (for patients with eosinophil counts ≥300/μL) will be used in the sample size reestimation and strictly no treatment information will be used in the review. The pooled study summaries will not contain any information that would potentially reveal the treatment assignments (e.g., post-randomization eosinophil levels). The review will be conducted before the last patient with eosinophil counts ≥300/μL is randomized. The exacerbation rate and shape parameter will be estimated using the maximum likelihood approach as proposed by Friede and Schmidli 2010. This review may result in an increase of sample. Since this review will be performed in a blinded fashion, no adjustment for the type I error is needed. The blinded data review will be performed by AstraZeneca internal personnel or its designees and the full details of the review will be specified in a blinded data review plan.

8.3 Definitions of analysis sets

All efficacy analyzes will be performed using an Intent-to-Treat (ITT) approach based on the full analysis set. For consistency, demographic and baseline characteristics will be presented using the full analysis set. Safety objectives will be analyzed based on the Safety population.

8.3.1 All patients analysis set

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

8.3.2 Full analysis set

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

8.3.3 Safety analysis set

All patients who received at least 1 dose of IP will be included in the safety analysis set. Patients will be classified according to the treatment they actually received. A patient who has on one or several occasions received active treatment will be classified as active. If a patient has received both active dose regimens, then the patient will be classified as the higher active dose regimen. All safety summaries will be based on this analysis set.

8.3.4 Pharmacokinetic analysis set

All patients who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations and who had at least one quantifiable serum PK observation post first dose will be included in the PK analysis dataset. All PK summaries will be based on this analysis set.

8.4 Variables for analyses

8.4.1 Calculation or derivation of efficacy variables

All efficacy objectives will be evaluated for the double-blind treatment period, defined as the period after administration of randomized IP at Visit 4 and the conclusion of EOT visit, inclusive.

8.4.1.1 Exacerbation rate

The annual asthma exacerbation rate will be used as the primary 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 56-week 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 OCS 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 OCS 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 double-blind treatment period will be used as response variable.

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

Maximum follow-up time for a patient is approximately 56 weeks; defined as the time from randomization to the date of Visit 19. 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.

In the statistical analysis, the number of asthma exacerbations experienced by a patient during the 56-week double-blind treatment period will be used as response variable, and the logarithm of the patient's corresponding follow-up time will be used as an offset in the analysis to adjust for patients having different exposure times during which the events occur.

For the production of summary statistics, the annual exacerbation rate per patient is calculated, and standardized using data from the 56-week double-blind treatment period according to the formula described below.

*Annual Exacerbation Rate=Number of Exacerbations*365.25/(Follow-up date-Visit 4 date+1).*

8.4.1.2 Proportion of patients with ≥1 asthma exacerbation during 56 weeks of treatment

The proportion of patients with ≥ 1 asthma exacerbation during the 56 weeks of treatment will be a supportive variable to the primary objective.

8.4.1.3 Time to first exacerbation

Time from randomization to the first asthma exacerbation will also be used as a supportive variable to the primary objective, and is calculated as follows:

Start Date of first asthma exacerbation-Date of Randomization+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 56-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients).

8.4.1.4 Forced expiratory volume in 1 second

Pre-BD FEV_1 is a key secondary efficacy endpoint of this study, and the change from baseline to Week 56 is included in the multiple testing strategy.

The change from baseline to each of the post-randomization visits (post Visit 4) up to and including the end of 56-week double-blind treatment visit (Visit 19) will be used as secondary efficacy variables. The pre-BD measurement recorded at Visit 4 will be used as baseline FEV_1. If the Visit 4 pre-BD measurement is missing, the last non-missing pre-BD value before Visit 4 will be used as baseline instead.

8.4.1.5 Annual rate of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalization

The annual rate of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalization, as determined by an independent adjudication committee (as described in Section 8.6) will be a secondary efficacy variable.

The number of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalization experienced by a patient during the 56-week treatment period will be derived according to the following rule:

The number of asthma exacerbations experienced by a patient during the 56-week treatment period will be derived according to rule for the primary outcome variable in Section 2.

In the statistical analysis, the number of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalization experienced by a patient during the 56-week double-blind treatment period will be used as response variable, and the logarithm of the patient's corresponding follow-up time will be used as an offset in the analysis to adjust for patients having different exposure times during which the events occur.

Maximum follow-up time is approximately 56 weeks, and the follow-up time is derived as described in Section 8.4.1.1.

Additionally, for the production of descriptive statistics, the annualized rate of asthma-related emergency room/urgent care visits and hospitalizations will be calculated using the same methodology as the annualized rate of exacerbations described in Section 8.4.1.1.

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, haematology, clinical chemistry, urinalysis, and reported AEs.

Change from baseline (Visit 4) to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. AEs will be summarized by means of descriptive statistics and qualitative summaries.

8.4.2.2 Other significant adverse events

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

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

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

8.4.3 Calculation or derivation of patient reported outcome variables

8.4.3.1 Asthma symptom score

The outcome variable for asthma symptom score will be the change in mean Q1 asthma symptom score from baseline (Visit 4) to each of the post-randomization periods. Asthma symptom daytime score, night time score, and total score will be calculated separately.

Total asthma symptom score is a key secondary efficacy endpoint of this study, and the change from baseline to Week 56 is included in the multiple testing strategy.

8.4.3.2 Asthma Control Questionnaire (ACQ-6)

The outcome variable for ACQ-6 will be the change in mean score from baseline (Visit 4) to each of the post-randomization periods.

Patients will also 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.

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

Furthermore, patients will 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

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

The AQLQ(S)+12 score will be summarized by domain (4 domains) and for overall. The outcome variable for the AQLQ(S)+12 will be the change in mean score from baseline (Visit 4) to each of the post-randomization periods.

Patients will also be categorized according to the following limits:

- 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.

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

8.4.3.4 Electronic diary variables

Asthma PROs (ACQ-6, AQLQ(S)+12, EQ-5D-5L, WPAI+CIQ), and daily metrics (rescue medication, awakenings and peak flow and asthma symptom scores) derived from the Asthma Daily Diary will be summarized as the mean for baseline period and each of the post-randomization periods.

Baseline is defined as the last non-missing value before randomization for the asthma PROs and as the last 10 days before randomization for the daily metrics. Each post-randomization

period is defined as the period between 2 consecutive scheduled visits (till Week 56 Visit). The change from baseline to each post-randomization period will be used as secondary efficacy variables.

Rescue medication usage is captured in the daily diary as the number of inhaler puffs and the number of times a nebulizer is used. Rescue medication usage will be summarized as the number of puffs with one instance of nebulizer use converted to two puffs.

8.4.4 Calculation or derivation of pharmacokinetic variables

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

The PK data will be merged with those from other clinical studies for a population-based meta-analysis. Results of the meta-analysis will be presented in a separate pharmacometrics report outside of the CSR.

8.4.5 Calculation or derivation of immunogenicity variables

ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer). All ADA positive samples with the exception of those from Week 8 from the study will be tested for nAb using a ligand binding assay.

8.5 Methods for statistical analyses

The analysis of the primary and secondary endpoints will include all data captured during the 56-week treatment period, including follow-up (when applicable), unless the patient withdraws consent, and assent when applicable, to study participation, regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence.

Testing strategy to account for multiplicity considerations

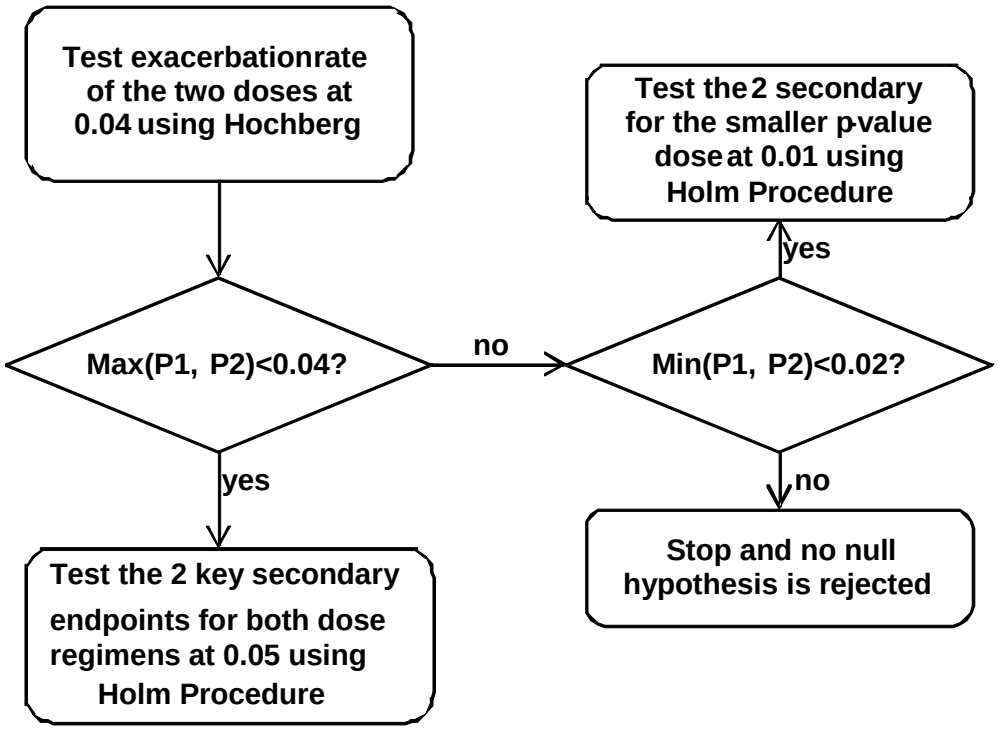
To account for multiplicity to test the primary (annual asthma exacerbation rate) and 2 key secondary endpoints (the change in FEV_1 and asthma symptom score from baseline to Week 56, respectively) for each of the 2 dosing regimens (for high-dose-ICS patients with baseline blood eosinophils $\geq 300/\mu L$) a testing strategy will be followed to control the overall type I error rate. The testing strategy will be according to the following gate-keeping procedure:

Step 1: Perform the 2 tests of annual asthma exacerbation rate (one test for each dose regimen vs placebo) at the family wise error rate (FWER) of 0.04 using a Hochberg Procedure (Hochberg 1988). If both p-values are less than 0.04, then proceed to Step 2; else if the smaller p-value is less than 0.02 then proceed to Step 2a; otherwise no null hypothesis is rejected

Step 2: Test the 2 key secondary endpoints for both dose regimens as one family at the FWER of 0.05 using a Holm Procedure (Holm 1979).

Step 2a: Test the two secondary endpoints for the smaller-p-value dose at the FWER of 0.01 using a Holm Procedure.

The gate-keeping procedure is also shown in the diagram below:



Since the correlation of the 2 test statistics for asthma exacerbation rate in the Step 1 is positive, due to the common placebo group, the FWER of the Hochberg Procedure is strongly controlled at 0.04. The overall FWER of the gate keeping procedure is strongly controlled at 0.05.

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

8.5.1 Primary analysis method(s)

The primary efficacy variable is the annual asthma exacerbation rate and the primary analysis is to compare the annual asthma exacerbation rate of each benralizumab dose regimen with placebo in high-dose-ICS patients with baseline blood eosinophil counts ≥300/μL.

For each of the 2 benralizumab dose regimens, the null hypothesis is that the exacerbation rate on benralizumab is equal to the exacerbation rate on placebo. The alternative hypothesis is that the exacerbation rate on benralizumab is not equal to the exacerbation rate on placebo, ie,

H0: Rate ratio (benralizumab vs Placebo) = 1
Ha: Rate ratio (benralizumab vs Placebo) ≠ 1

Exacerbation rate in each of the 2 benralizumab dose regimen groups will be compared to exacerbation rate in the placebo group using a negative binomial model. The response variable in the model will be the number of asthma exacerbations over the 56-week treatment period. The model will include covariates of treatment group, country, number of exacerbations in the year before the study, and the use of maintenance OCS (yes/no). The logarithm of the follow-up time will be used as an offset variable in the model.

The estimated treatment effect (ie, the rate ratio of benralizumab versus placebo), corresponding 95% confidence interval (CI), and two-sided p-value for the rate ratio will be presented. In addition, the exacerbation rate and the corresponding 95% CI within each treatment group will be presented.

In addition, the exacerbation rate will also be summarized in patients with baseline blood eosinophil counts <300/μL, <150/μL, 150-299/μL 300-449/μL, and ≥450/μL separately for descriptive purpose only.

The above analyses of exacerbation rate will also be performed for the medium-dose-ICS patients and the combined population of high and medium dose patients separately while the multiplicity will not be adjusted for these analyses. The analyses for the combined population of high and medium dose patients will also have the ICS dose (high/medium) as a covariate.

The individual exacerbation criteria (ER visit due to asthma that required systemic corticosteroids, hospitalization due to asthma, or use of systemic corticosteroids) will also be summarized descriptively.

8.5.2 Secondary analysis methods

8.5.2.1 Analysis methods for secondary efficacy variables

Key secondary efficacy endpoints in this study are:

- Change from baseline in pre-BD FEV1 at Week 56
- Change from baseline in asthma symptom total score at Week 56

Other secondary efficacy endpoints include

- Proportion of patients with ≥1 asthma exacerbation
- Time to the first asthma exacerbation
- Annual rate of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalization
- Change from baseline in total rescue medication use (average puffs/day)
- Change from baseline in post-bronchodilator FEV1 at Week 56
- Change from baseline in morning and evening PEF at Week 56
- Change from baseline in asthma symptom daytime/nighttime scores at Week 56

- Change from baseline in number of in number of nights with awakening due to asthma and requiring rescue medication
- ACQ-6
- AQLQ(S)+12
- WPAI+CIQ
- EQ-5D-5L
- CGIC
- PGIC

All the secondary efficacy endpoints will be analyzed in patients with baseline blood eosinophil counts ≥300/μL. In addition, the 2 key secondary efficacy endpoints will be analyzed in patients with baseline blood eosinophil counts <150/μL, <300/μL, 150-299/μL, 300-449/μL and ≥450/μL separately for descriptive purpose only. These analyses will also be performed for medium-dose-ICS patients and the combined population of high and medium dose patients separately while the multiplicity will not be adjusted. The analyses for the combined population of high and medium dose patients will also have the ICS dose (high/medium) as a covariate.

Change from baseline in pre-BD FEV_1 at Week 56 will be compared between each of the 2 benralizumab dose regimen groups and placebo using a repeated measures analysis on patients with a baseline pre-BD FEV_1 and at least 1 post-randomization pre-BD FEV_1 in the full analysis set. The dependent variable will be the change from baseline in pre-BD FEV_1 at post-baseline protocol-specified visits (up to the EOT Visit). Treatment group will be fitted as the explanatory variable, and country, baseline pre-BD FEV_1, and the use of maintenance OCS (yes/no) will be fitted as covariates. Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is:

*Change in FEV_1=Treatment group+baseline FEV_1+country +maintenance OCS+ visit+ treatment*visit*

Change from baseline in asthma symptom total score; daytime score, and nighttime score at Week 56 will be analyzed separately using a similar model as the above model for change from baseline in pre-BD FEV_1.

The proportion of patients with ≥1 asthma exacerbation during the 56 weeks of treatment will be addressed as a supportive variable to the primary objective. The proportion in each of the 2 benralizumab dose regimen groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for country, number of exacerbations in the year before the study, and the use of maintenance oral corticosteroids (yes/no).

Time to first asthma exacerbation will be analyzed as another supportive efficacy variable to the primary objective to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment, country, number of exacerbations in the year before the study, and the use of maintenance OCS (yes/no).

Annual rate of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalization will be analyzed using a similar Negative binomial model as outlined for the primary efficacy variable in Section 8.5.1.

Change from baseline in total rescue medication use (average puffs/days) and number of nights with awakening due to asthma and requiring rescue medication will be analyzed using a similar model as for change from baseline in pre-BD FEV_1.

Change from baseline in post-BD FEV_1, morning and evening PEF at Week 56 will be analyzed separately using similar models as the model for change from baseline in pre-bronchodilator FEV_1.

The ACQ-6 and AQLQ(S)+12 will be analyzed in terms of change from baseline to end of treatment, change from baseline to overall post-baseline mean, and responders as defined by each of ACQ-6 and AQLQ(S)+12 scores.

Change in mean score from baseline for ACQ-6 and AQLQ(S)+12 (including the domain scores) will be analyzed using a similar model as for change from baseline in pre-BD FEV_1.

Responder variables for ACQ-6 (yes/no) and AQLQ(S)+12 (yes/no) will be analyzed using a logistic regression model with covariates of treatment, country, baseline value, and the use of maintenance oral corticosteroids (yes/no).

The EQ-5D-5L and WPAI+CIQ will be summarized by treatment.

CGIC and PGIC will be summarized by treatment group and visit.

8.5.2.2 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 haematology 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.

8.5.2.3 Analysis methods for pharmacokinetic variables

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

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

To further characterize the pharmacokinetic properties of benralizumab, the PK data will be merged with those from other clinical studies for a population-based meta-analysis. The population modeling results will be presented in a separate pharmacometrics report outside of the CSR.

8.5.2.4 Analysis method for immunogenicity variables

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

8.5.3 Subgroup analysis

To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analyses and statistical modeling including testing for interaction between treatment and covariates will be performed in patients with baseline blood eosinophil counts ≥300/μL for the following factors: OCS use at baseline (yes/no), gender, age (<18, ≥18-65 and ≥65 years), geographic region, BMI (≤35, >35 kg/m2), the number of exacerbations during the previous year (2, 3, ≥4 exacerbations), and race. Data will be analyzed by Negative Binomial regression similar to the primary analysis and the same output will be presented for each subgroup as for the primary analysis. For the statistical modeling including interaction effects, the estimate of the interaction effects will be presented together with the corresponding p-value. These analyses are to be considered as exploratory and will be performed on the full analysis set.

8.5.4 Sensitivity analysis

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

8.5.5 Interim analysis

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

8.6 Independent adjudication committee

Benralizumab is being developed for the treatment of severe asthma. There is considerable variation in the reasons that patients seek emergency department care and in the clinical thresholds used to determine the need for hospitalization.

An independent adjudication committee, blinded to the treatment of the patients, will evaluate all emergency department visits and/or hospitalizations occurring from randomization during the course of the study to determine whether any were due to asthma-related exacerbations. The committee, which will include pulmonologists and or allergists/immunologists, will operate in accordance with an Adjudication Committee Charter/Manual of Operations which will also provide detail on what specific information the committee require to enable thorough adjudication.

8.7 Independent adjudication committee for major adverse cardiac events and malignancies

An independent adjudication committee will be constituted to provide an independent, external, systematic, and unbiased assessment of blinded data to confirm the 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.

8.8 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 centre personnel

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

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

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

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study centre, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent, and assent when applicable, of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent, and assent when applicable, 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 centre 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 centre personnel will be responsible for entering data on the observations, tests, and assessments specified in the CSP into the WBDC system and according to eCRF instructions. The eCRF instructions will also guide the study centre 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 centre.

9.2.3 Study agreements

The Principal Investigator at each/the study centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol 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 Clinical Study Agreement shall prevail.

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

9.2.4 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

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

The study is expected to start in Q3 2013 and to end by Q1 2016.

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

9.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Centre 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 Centre.

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 Clinical Study Agreement. The Investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study centre.

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

10.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form, and assent when applicable, 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 centre 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 Form, and assent when applicable, 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 Form, and assent when applicable, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca will provide Regulatory Authorities, 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 investigational product. 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 centre 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 centre's Informed Consent Form, and assent when applicable, AstraZeneca and the study centre's Ethics Committee are to approve the revised Informed Consent Form, and assent when applicable, 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

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the study centre, 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, analysed, 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 centre.

11. LIST OF REFERENCES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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