AstraZeneca

Revised Clinical Study Protocol 2

Drug Substance	Benralizumab (MEDI-563)
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A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β_2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative

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	10 April 2015		
2	10 February 2016		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change
1	26 August 2015		

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures.

PROTOCOL SYNOPSIS

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) to Reduce Oral Corticosteroid Use in Patients with Uncontrolled Asthma on High Dose Inhaled Corticosteroid plus Long-acting β_2 Agonist and Chronic Oral Corticosteroid Therapy (ZONDA)

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

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Study center(s) and number of patients planned

This study will be conducted worldwide in approximately 100 study centers. Target is to randomize approximately 210 patients.

Study period		Phase of development
Estimated date of first patient enrolled	Q2 2014	Phase 3
Estimated date of last patient completed	Q3 2016	

(a) Primary Objective

Objective	Endpoint [a]
To compare the effect of 2 dosing regimens of benralizumab on percentage reduction of oral corticosteroid (OCS) dose in adult patients with uncontrolled asthma	Percentage reduction in final OCS dose compared with baseline (Visit 6), while maintaining asthma control

(b) Secondary Objectives

Objective	Endpoint [a]
To assess the effect of 2 dosing regimens of benralizumab on OCS dose in adult patients with uncontrolled asthma	• Proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control • Proportion of patients with 100% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control • Proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control • Proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
To assess the effect of 2 dosing regimens of benralizumab on parameters associated with asthma exacerbations	• Proportion of patients with ≥1 asthma exacerbation after randomization • Annual rate of asthma exacerbations after randomization • Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization after randomization • Time to first asthma exacerbation after randomization • Time to first exacerbation requiring hospitalization • Time to first exacerbation requiring hospitalization or emergency department [ED] visit • Number of days in hospital due to asthma • Mean number of days with oral corticosteroids taken for exacerbations

Objective	Endpoint [a]
To assess the effect of 2 dosing regimens of benralizumab on pulmonary function	• Change from baseline in pre-bronchodilator forced expiratory flow in 1 second (FEV_1)
To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics	• Change from baseline in asthma symptom score (total, daytime, and night time) • Change from baseline in rescue medication use • Change from baseline in home lung function (morning and evening peak expiratory flow [PEF]) • Change from baseline in the number of nights with awakening due to asthma requiring rescue medication • Change from baseline in Asthma Control Questionnaire (ACQ-6)
To assess the effect of 2 dosing regimens of benralizumab on asthma related health-related quality of life	• Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ[S]+12)
To evaluate the pharmacokinetics (PK) and immunogenicity of 2 dosing regimens of benralizumab	• PK parameters • Anti-drug antibodies (ADA)
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels	• Blood eosinophils
To assess the impact of 2 dosing regimens of benralizumab on lung function as assessed through body plethysmography (subset of patients)	• Total lung capacity (TLC) • Residual volume (RV) • Vital capacity (VC) • Inspiratory capacity (IC) • Functional residual capacity (FRC)

(c) **Safety Objective**

Objective	Endpoint [a]
To assess the safety and tolerability of 2 dosing regimens of benralizumab	• Adverse events (AEs)/Serious adverse events (SAEs) • Laboratory variables • Electrocardiogram (ECG) • Physical Examination

(d) **Exploratory Objectives**

Objective	Endpoint [a]
To assess the impact of 2 dosing regimens of benralizumab on eosinophil progenitor cells (subset of patients)	• Assessment of eosinophil progenitor cells in blood
To assess the impact of 2 dosing regimens of benralizumab on sputum differential cell count and biomarkers (subset of patients)	• Sputum cell differential count • Quantification of sputum cytokines and biomarkers • Assessment of eosinophil progenitor cells in sputum
To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers	• Serum biomarkers

[a] Please note: Baseline for all endpoints will be Visit 6.

Study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate efficacy and safety of a fixed 30 mg dose of benralizumab administered subcutaneously (SC) in 2 dosing regimens (every 4 weeks [Q4W] throughout the treatment period, versus every 4 weeks for the first 3 doses and then every 8 weeks [Q8W] thereafter) in patients with uncontrolled asthma receiving high-dose inhaled corticosteroid (ICS)/long-acting β_2 agonist(LABA) and OCS with or without additional asthma controller(s).

The study will recruit approximately 210 patients (randomized 1:1:1), stratified by eosinophil level (≥150 to <300 vs ≥300 cells/μL) and country/region. **Approximately 60 patients will be randomized into the lower eosinophil stratum (≥150 to <300/μL). Approximately 150 patients will randomize into the higher eosinophil stratum (≥300 cells/μL).**

After enrolment and initial confirmation of entry criteria, patients will have an 8-week run-in/optimization period during which time the patient's dose of OCS will be titrated to the minimum effective dose without losing asthma control (optimized OCS dose). Patients who meet eligibility criteria will be randomized to a 28-week treatment period, with the last dose of benralizumab/placebo administered at Week 24, and an end-of-treatment (EOT) visit at Week 28. The treatment period is divided into 3 phases:

- Induction (from Week 0 to Week 4; patients will remain on the optimized OCS dose)
- Reduction (from Week 4 to Week 24, inclusive; OCS dose reduction will be initiated at Week 4 with following dose reduction at 4-week intervals)
- Maintenance (after Week 24 until Week 28; the dose of OCS reached at Week 24 or complete elimination of OCS will be maintained). Follow-up visits will be conducted at Week 36 (Visit 15) unless the patient decides to continue into a separate extension study; patients who remain on investigational product (IP) for the double-blind treatment period as defined in the protocol (see Section 1.5) may be eligible to enrol in

the follow-on extension study (these patients will not attend the Follow-up visit at Week 36).

The IP will be administered at the study center every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter. After the first 3 doses, patients randomized to the 8-week regimen will receive placebo at Visit 10 (Dose 4) with active drug administered at Visit 11 (Dose 5) and then every second treatment visit thereafter; placebo (dummy) injections will be administered at the 4-week interim treatment visits in order to maintain the blind.

Patients will be maintained on their currently prescribed high-dose ICS/LABA therapy, without change, from enrolment throughout the run-in and treatment period.

Target patient population

Male and female patients aged from 18 to 75 years with diagnosed asthma, willing to provide informed consent, and requiring continuous treatment with high-dose ICS (>500 mcg fluticasone dry powder formulation equivalents total daily dose) plus LABA and chronic OCS therapy.

Investigational product, dosage and mode of administration

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

Comparator, dosage and mode of administration

Matching placebo solution for injection in an APFS will be administered at the study center SC every 4 weeks.

Duration of treatment

Following initial enrolment at Week -10, the patient will enter a 10-week enrolment, run-in/optimization phase which is followed by a 28-week double-blind, randomized treatment period, with the last dose of benralizumab/placebo administered at Week 24 and an EOT visit at Week 28. A follow-up visit will be conducted at Week 36.

The total planned study duration is up to 46 weeks.

Patients who remain on IP for the double-blind treatment period as defined in the protocol (see Section 1.5) may be eligible to enrol in the follow-on extension study (these patients will not attend the Follow-up visit at Week 36).

Statistical methods

The primary efficacy variable is the percentage change in OCS dose from the patient's dose at baseline to the patient's final dose at Visit 14, while maintaining asthma control. The percentage change in OCS in each of the 2 benralizumab dose regimen groups will be compared with the percentage reduction in OCS in the placebo group using a Wilcoxon rank sum test. Multiplicity will be adjusted using Hochberg procedure (Hochberg 1988).

For the following variables, 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/region: the proportion of patients with ≥1 asthma exacerbation during the 28 weeks of treatment; the proportion of patients with ≥50% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with 100% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control.

Annual exacerbation rates will be analyzed using a negative binomial model with a log-link function. The model will include covariates of treatment group, country/region, and number of exacerbations in the year before the study. Annual exacerbation rates that are associated with an emergency room visit or a hospitalization will be analyzed similarly to annual rate of asthma exacerbations.

Time to first asthma exacerbation will be analyzed using a Cox proportional hazard model with the covariates of treatment, country/region and number of exacerbations in the year before the study. Time to first asthma exacerbation requiring hospitalization and time to first asthma exacerbation requiring hospitalization or ED visit will be analyzed similarly to time to first asthma exacerbation.

Change from baseline in pre-bronchodilator (pre-BD) FEV_1 will be analyzed using a repeated measures analysis model which will include treatment group country/region and baseline pre-BD FEV_1 as covariates. Visit will be fitted as a categorical variable. The following variables will be analyzed similarly to change from baseline in pre-BD FEV_1: Change from baseline in asthma symptom total score, daytime score, night time score, total rescue medication use, change from baseline in number of nights awakening due to asthma requiring rescue medication use, change from baseline in morning and evening PEF, and the change from baseline in ACQ-6 and AQLQ(s)+12.

The study will recruit a total of 210 patients with blood eosinophils ≥150 to <300 and ≥300/μL. As the targeted patient population for the pivotal studies is ≥300 eosinophils/μL, this study will be stratified by ≥300 and ≥150 to <300 cells/μL. The eosinophil ≥150 to <300/μL stratum will randomize approximately 60 patients and the ≥300 cells/μL stratum will randomize approximately 150 patients. For sample size estimation, 70 patients per treatment arm are required to detect a difference in percent reduction of OCS dose each of the benralizumab groups and the placebo group with 86% power using a two-sided 5% level Wilcoxon rank sum test. The sample size calculation is based on simulations using the OCS reduction data from Steroid Reduction with Mepolizumab Study (SIRIUS) (Bel et al 2014) which showed a median percentage reduction of 50% in the active treatment group compared with no reduction in the placebo group.

Results for exploratory variables will be summarized using descriptive statistics by treatment group.

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.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AQLQ(S)+12	Standardized 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
CI	Confidence interval
CO_2	Carbon dioxide
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency department
EOT	End of treatment
ePRO	Electronic patient reported outcome
FEV_1	Forced expiratory volume in 1 second
FRC	Functional residual capacity
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
Gamma-GT	Gamma-glutamyl transpeptidase

Abbreviation or special term	Explanation
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
HCP	Health care provider
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
IC	Inspiratory capacity
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICI	International Coordinating Investigator
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
IP	Investigational product
IPD	Premature investigational product discontinuation
IRV	Inspiratory Reserve Volume
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-acting β_2 agonists
LTRA	Leukotriene receptor antagonists
MedDRA	Medical Dictionary for Regulatory Activities
OCS	Oral corticosteroids
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
PN	Predicted normal
Post-BD	Post-bronchodilator
Pre-BD	Pre-bronchodilator

Abbreviation or special term	Explanation
RBC	Red blood cell
RV	Residual volume
SABA	Short-acting β_2 agonists
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
TLC	Total lung capacity
ULN	Upper limit of normal
UNS	Unscheduled
VC	Vital capacity
WBC	White blood cell
WBDC	Web-based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background

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

The current approach to anti-inflammatory controller therapy in asthma is based on a step–wise intensification of a daily maintenance regimen primarily centered around inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA), with the addition of long–acting β_2 agonists (LABA) in patients with more severe asthma (GINA 2014, NAEPP 2007). Despite treatment per management guidelines, up to 50% of patients have asthma that is not well-controlled (Barnes 1998, Barnes and Adcock 2003, Bateman et al 2010). This results in considerable impact on quality of life, disproportionate use of healthcare resources, and adverse reactions from regular systemic steroid use. Therefore, there remains an unmet medical need for patients whose asthma is not controlled by existing therapies.

The observed variability in clinical response to currently available asthma therapies appears to be related, in part, to distinctive inflammatory phenotypes (Wenzel 2012). In particular, asthma associated with eosinophilic inflammation in the airway (often referred to as eosinophilic asthma) is common (approximately 40% to 60% of asthmatics) with the degree of eosinophilia associated with clinical severity including the risk of asthma exacerbations (Bousquet et al 1990; Louis et al 2000; Di Franco et al 2003; Scott and Wardlaw 2006, Simpson et al 2006; Zhang and Wenzel 2007). 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 2011 and 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) to benralizumab which results in highly efficient eosinophil depletion by apoptosis (Kolbeck et al 2012). Single and repeated doses of benralizumab in mild to severe asthma patients during Phase 2 development resulted in depletion of blood and airway eosinophils, and improvement in multiple metrics of

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

1.2 Rationale for conducting this study

The treatment options for patients who remain uncontrolled on high-dose ICS-LABA are extremely limited; one of the treatment options is addition of the oral corticosteroids (OCS) to the current treatment (GINA 2014). However, regular intake of OCS leads to a number of adverse events (AEs) and as a result decreases quality of life for these patients (Kwong et al 1987).

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. Nair et al have demonstrated the steroid-sparing effects of anti-interleukin-5 therapy in OCS-dependent eosinophilic asthmatics, which serves as further support for the proposed mechanism of action of benralizumab in this difficult to treat population (Nair et al 2009).

The purpose of this trial is to confirm if benralizumab can reduce the use of maintenance OCS in systemic corticosteroid dependent patients with severe refractory asthma with elevated eosinophils.

In addition, this trial will further confirm the safety and clinical benefit of benralizumab compared with placebo on markers of asthma impairment and risk including exacerbation rate, pulmonary function, asthma symptoms, and asthma-related quality of life.

1.3 Rationale for study design, doses, and control groups

This is a global study designed to investigate the safety and efficacy of 2 dosing regimens of benralizumab (at a 30 mg fixed dose) administered subcutaneously (SC) in asthma patients who remain uncontrolled on chronic OCS and high-dose ICS-LABA therapy, with or without additional asthma controller(s). Patients on the first regimen will be dosed every 4 weeks (Q4W) throughout the treatment period, while patients on the second regimen will be dosed every 4 weeks for the first 3 doses and then every 8 weeks (Q8W) thereafter. Primary efficacy will be determined based on the percentage reduction in OCS dose over 24 weeks of benralizumab treatment versus placebo, following OCS dose optimization.

The study will recruit approximately 210 patients with blood eosinophils ≥150/μL. It is well established that corticosteroid administration can dramatically suppress blood eosinophil counts (Schleimer and Bochner 1994, Barnes 1998, Barnes and Adcock 2003), and some level of efficacy was seen in patients with peripheral blood eosinophil counts <300/μL from the 100 mg treatment arm Phase 2b study MI-CP220 (see Section 1.4); thus, the target population in this study will be patients with blood eosinophils ≥150/μL. In order to avoid biasing the

results, the study will be randomized and double-blinded, with additional stratification by country/region.

All patients are required to be treated with oral corticosteroids for at least 6 months prior to Visit 1 and be on the stable maintenance dose of prednisone or prednisolone for at least 2 weeks prior to randomization.

The benralizumab dose (30 mg SC, fixed) and the maintenance regimens are based on all available efficacy and safety data, as well as population exposure-response modeling and stochastic trial simulations from earlier phase benralizumab trials. In particular, Phase 2b MI-CP220 study showed that fixed doses of benralizumab ≥20 mg administered Q8W were clinically effective. Analyses of efficacy endpoints (asthma exacerbations, forced expiratory volume in 1 second [FEV_1] and Asthma Control Questionnaire [ACQ]) suggest 30 mg Q8W (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} for asthma exacerbation reduction and ACQ, and maintains a steady-state pharmacokinetic (PK) exposure close to EC_{90} levels for FEV_1 and ACQ.

Other stable asthma therapies on top of OCS and 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 2014). 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 (Phase 2b MI-CP220 study, based on the interim analysis). Clinical benefit appeared to be greatest in patients with blood eosinophil counts ≥300/μL; however, some level of efficacy (a 16% reduction in annual rate of asthma exacerbations) was seen in patients with peripheral blood eosinophil counts <300/μL from the 100 mg treatment arm of Study CP220 and should support a positive benefit/risk balance in this population. Furthermore, Bel et al saw a significant reduction in oral glucocorticoid dose with mepolizumab treatment in patients with blood eosinophil counts of 150/μL and above (Bel et al 2014).

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).

Blood 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 efficacy and safety of a fixed 30 mg dose of benralizumab administered SC in 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 patients with uncontrolled asthma receiving high-dose ICS-LABA and OCS with or without additional asthma controller(s).

The study will recruit approximately 210 patients (randomized 1:1:1) with eosinophils ≥150 cells/μL, stratified by eosinophil level (≥150 to <300 vs ≥300 cells/μL) and country/region.

After enrolment and initial confirmation of entry criteria, patients will have an 8-week run-in/optimization period during which time the patient's dose of OCS will be titrated to the minimum effective dose without losing asthma control. If the patient meets all of the criteria listed for OCS titration in Section 5.1.1.1, his/her asthma will be considered stable and the patient will be eligible for further OCS dose reduction. All patients must be on either oral prednisone or prednisolone as their OCS. Patients who are on any other oral corticosteroid must switch over to an equivalent dose of either oral prednisone or prednisolone at Visit 1. Patients who meet eligibility criteria will be randomized to a 28-week treatment period, with last dose of benralizumab/placebo administrated at Week 24 and end of treatment (EOT) visit at Week 28.

The treatment period is divided into 3 phases:

- Induction (from Week 0 to Week 4; patients will remain on the optimized OCS dose)

- Reduction (from Week 4 to Week 24, inclusive; OCS dose reduction will be initiated at Week 4 with following dose reduction at 4-week intervals)

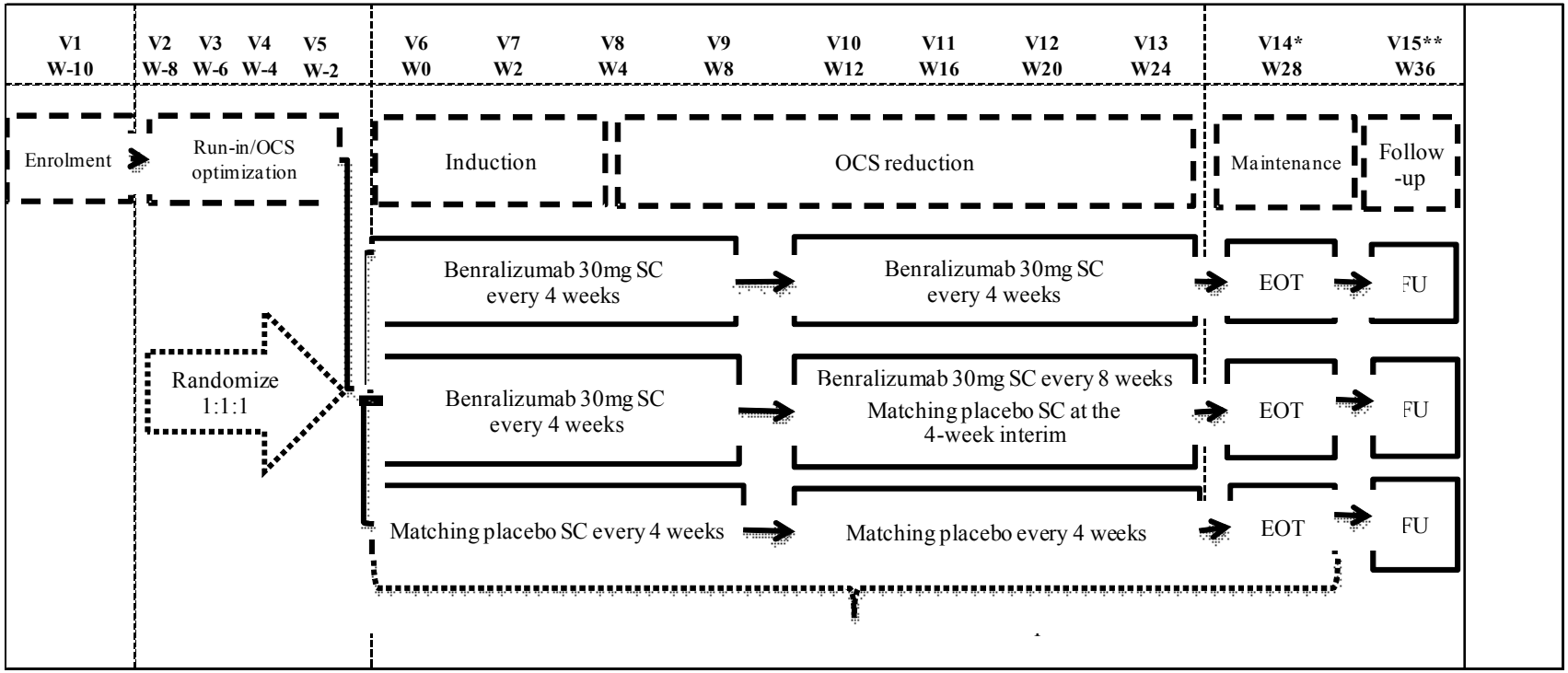
- Maintenance (after Week 24 to Week 28; the dose of OCS reached at Week 24 or complete elimination of OCS will be maintained).

A Follow-up visit will be conducted at Week 36 (Visit 15) unless the patient decides to continue into a separate extension study; patients who remain on IP for the double-blind treatment period as defined in the protocol (see Section 1.5) may be eligible to enrol in the follow-on extension study (these patients will not attend the Follow-up visit at Week 36).

The investigational product (IP) will be administered at the study center every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter. After the first 3 doses, patients randomized to the 8-week regimen will receive placebo at Visit 10 (Dose 4) with active drug administered at Visit 11 (Dose 5) and then every second treatment visit thereafter; placebo (dummy) injections will be administered at the 4-week interim treatment visits in order to maintain the blind.

Patients will be maintained on their currently prescribed high-dose ICS-LABA therapy, without change, from enrolment throughout the run-in and treatment period.

Figure 1 Study flow chart



*Patients entering the extension study (D3250C00021) will receive their first dose of benralizumab at Visit 1 in that study, which must occur on the same day as Visit 14 (EOT) for this study (D3250C00020).

**Only those patients not entering the extension study will complete this Follow-up visit.

2. STUDY OBJECTIVES

(a) Primary Objective

Objective	Endpoint [a]
To compare the effect of 2 dosing regimens of benralizumab on percentage reduction of oral corticosteroid (OCS) dose in adult patients with uncontrolled asthma	Percentage reduction in final OCS dose compared with baseline (Visit 6), while maintaining asthma control

(b) Secondary Objectives

Objective	Endpoint [a]
To assess the effect of 2 dosing regimens of benralizumab on OCS dose in adult patients with uncontrolled asthma	• Proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control • Proportion of patients with 100% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control • Proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control • Proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control

Objective	Endpoint [a]
To assess the effect of 2 dosing regimens of benralizumab on parameters associated with asthma exacerbations	• Proportion of patients with ≥1 asthma exacerbation after randomization • Annual rate of asthma exacerbations after randomization • Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization after randomization • Time to the first asthma exacerbation after randomization • Time to first exacerbation requiring hospitalization • Time to first exacerbation requiring hospitalization or emergency department (ED) visit • Number of days in hospital due to asthma • Mean number of days with oral corticosteroids taken for exacerbations
To assess the effect of 2 dosing regimens of benralizumab on pulmonary function	• Change from baseline in pre-bronchodilator (pre-BD) forced expiratory volume in 1 second (FEV_1)
To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics	• Change from baseline in asthma symptom score (total, daytime, and night time) • Change from baseline in rescue medication use • Change from baseline in home lung function (morning and evening peak expiratory flow [PEF]) • Change from baseline in the number of nights with awakening due to asthma requiring rescue medication • Change from baseline in Asthma Control Questionnaire (ACQ-6)
To assess the effect of 2 dosing regimens of benralizumab on asthma related health-related quality of life	• Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ[S]+12)
To evaluate the pharmacokinetics (PK) and immunogenicity of 2 dosing regimens of benralizumab	• PK parameters • Anti-drug antibodies (ADA)
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels	• Blood eosinophils

Objective	Endpoint [a]
To assess the impact of 2 dosing regimens of benralizumab on lung function as assessed through body plethysmography (subset of patients)	• Total lung capacity (TLC) • Residual volume (RV) • Vital capacity (VC) • Inspiratory capacity (IC) • Functional residual capacity (FRC)

(c) **Safety Objective**

Objective	Endpoint [a]
To assess the safety and tolerability of 2 dosing regimens of benralizumab	• Adverse events (AEs)/Serious adverse events (SAEs) • Laboratory variables • Electrocardiogram (ECG) • Physical Examination

(d) **Exploratory Objectives**

Objective	Endpoint [a]
To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels (subset of patients)	• Assessment of eosinophil progenitor cells in blood
To assess the impact of 2 dosing regimens of benralizumab on sputum differential cell count and biomarkers (subset of patients)	• Sputum cell differential count • Quantification of sputum cytokines and biomarkers • Assessment of eosinophil progenitor cells in sputum
To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers	• Serum biomarkers

[a] Please note: Baseline for all endpoints will be Visit 6.

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. Provision of informed consent prior to any study specific procedures

2. Female and male aged from 18 to 75 years, inclusively

3. Women of childbearing potential (WOCBP) must use a highly effective form of birth control (confirmed by the Investigator). Highly effective forms of birth control include: true sexual abstinence, a vasectomized sexual partner, Implanon, female sterilization by tubal occlusion, any effective IUD Intrauterine device/IUS Ievonorgestrel Intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch ™ or Nuvaring™. Women of childbearing potential must agree to use highly effective method of birth control, as defined above, from enrolment, throughout the study duration, and to within 16 weeks after last dose of IP, and have a negative serum pregnancy test result on Visit 1.

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

   - Women <50 years old will 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 will 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. Peripheral blood eosinophil count of ≥150 cells/μL assessed by local lab at Visit 1

7. 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. Equivalents for fluticasone dry powder can be found in Appendix E

8. Documented treatment with high-dose ICS (>500μg fluticasone propionate dry powder formulation equivalents total daily dose) and LABA for at least 6 months prior to Visit 1. The ICS and LABA can be contained within a combination product or given by separate inhalers:

- In order to aid the dose assessment, ICS equivalents for high-dose fluticasone propionate dry powder, as published by the Global Initiative for Asthma (GINA) guidelines, are presented in Appendix E

- For ICS/LABA combination preparations, the highest approved maintenance dose in the local country will meet this ICS criterion

9. Chronic oral corticosteroid therapy for at least 6 continuous months directly preceding Visit 1. Subjects must be on doses equivalent to 7.5 – 40 mg/day of prednisolone/prednisone at Visit 1 and be on a stable dose for at least 2 weeks prior to randomization. In order to aid the dose assessment, a guide for OCS dose equivalence is presented in Appendix H. Patients must agree to switch to study-required prednisone/prednisolone as their oral corticosteroid for the duration of the study.

10. Patients with documented failures of OCS reduction within 6 months prior to Visit 1 will not be required to proceed through the dose optimization phase during run-in. Failed attempts at OCS dose reduction are those which resulted in documented clinical deterioration or reduced lung function attributed to asthma, defined as:

    - Pre-BD FEV_1 < 80% of personal baseline

    - Morning PEF < 80% of personal baseline

    - Night time awakenings increase of > 50% of mean personal baseline

    - Albuterol, salbutamol use > 4 puffs/day above mean personal baseline

    - Requirement for a prednisone or prednisolone burst (large temporary increase) to treat an asthma exacerbation provoked by steroid reduction

11. Additional maintenance asthma controller medications (eg, LTRAs, tiotropium, cromone, theophylline), are allowed. Five-lipoxygenase inhibitors (eg, zileuton and roflumilast) are prohibited

12. Morning pre-BD FEV_1 of <80% predicted at Visit 2 (Week -8)

13. Evidence of asthma as documented by either:

    - Airway reversibility (FEV_1 ≥12% and 200 mL) demonstrated at Visit 1, Visit 2, or Visit 3 using the Maximum Post-bronchodilator Procedure OR

    - Documented reversibility in the previous 24 months prior to Visit 1 OR

- Airway hyperresponsiveness (PC_{20} FEV_1 methacholine concentration ≤8mg/mL) documented in the previous 12 months prior to planned date of randomization OR

- Airflow variability in clinic FEV1 ≥20% between 2 consecutive clinic visits documented in the 12 months prior to the planned date of randomization (FEV_1 recorded during an exacerbation should not be considered for this criterion).

Note: **All patients must have reversibility testing performed before randomization to establish a baseline characteristic.**

If patients do not demonstrate airway reversibility at either Visit 1 or Visit 2 and this is needed to qualify the patient for randomization, the site should reiterate the need to withhold short- and long-acting bronchodilators as required in Section 5.1.3 prior to Visit 3 in an effort to meet this inclusion criterion.

14. At least 1 documented asthma exacerbation in the previous 12 months prior to the date informed consent is obtained (please refer to Section 4.1.1)

Inclusion criteria at randomization

15. For WOCBP only: have a negative urine pregnancy test at Visit 6

16. Optimized OCS dose reached at least 2 weeks prior to randomization

17. Additional asthma controller medication must not have been initiated during run in/optimization period (not applicable for management of exacerbations during screening/ run in optimization phase)

18. At least 70% compliance with OCS use from Visit 1 to Visit 6 based on the Asthma Daily Diary

19. At least 70% compliance with usual asthma controller ICS-LABA from Visit 1 to Visit 6 based on Asthma Daily Diary

20. Minimum 70% (ie, 10 of 14 days) compliance with Asthma Daily Diary (morning and evening diary) for the period between each study visit from Visit 1 to Visit 6

3.2 Exclusion criteria

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

1. Clinically important pulmonary disease other than asthma (eg, active lung infection, Chronic obstructive pulmonary disease (COPD), bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are

associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome)

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

   – Affect the safety of the patient throughout the study

   – Influence the findings of the studies or their interpretations

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

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

4. History of anaphylaxis to any biologic therapy

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

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

7. Any clinically significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry, or urinalysis during run-in/optimization 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 run-in/optimization 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 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 was obtained

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

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 is obtained. Chronic maintenance OCS for the treatment of asthma is allowed.

15. Clinically significant asthma exacerbation, in the opinion of the Investigator, including those requiring use of systemic corticosteroids, or an increase in maintenance dose of OCS 2 weeks prior to the date of informed consent.

16. History of life-threatening asthma

17. Asthma control reached at an OCS dose of ≤5mg during run-in/OCS optimization phase (Visit 2 to Visit 6)

18. Qualifies for 3 consecutive dose reductions at Visits 2-4 and continues to meet OCS dose reduction criteria at Visit 5

19. Receipt of oral corticosteroids, other than prednisone or prednisolone, as the maintenance oral steroid controller for asthma symptoms from Visit 1 and throughout the study.

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

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

22. Receipt of live attenuated vaccines 30 days prior to Visit 1

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

23. Receipt of any investigational nonbiologic within 30 days or 5 half-lives prior to Visit 1 is obtained, whichever is longer

24. Patients previously randomized and dosed in any benralizumab clinical trial

25. Initiation of new allergen immunotherapy is not allowed within 30 days prior to Visit 1. Immunotherapy initiated prior to this period, or as a routine part of the patient's seasonal treatment, is allowed. If the immunotherapy is delivered as an injection, there should be a gap of 7 days between the immunotherapy and IP administration

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

27. Planned surgical procedures during the conduct of the study

28. Currently breastfeeding or lactating women

29. Previous randomization in the present study

30. Concurrent enrolment in another clinical trial

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

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

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

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

3.3 Patient enrolment and randomization

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

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

The Investigator will:

1. Obtain signed informed consent 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

Patients will be allocated to 1 of 3 treatment arms in a 1:1:1 ratio. The randomization will be stratified by eosinophil level (≥150 to <300 vs ≥300 cells/μL) and country/region and the randomization numbers will be grouped in blocks.

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

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 to not meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

If a patient that does not meet all the eligibility criteria is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca Physician immediately.

The AstraZeneca Physician must ensure all such contacts are appropriately documented.

3.5 Concomitant medications, restrictions during and after the study

3.5.1 Concomitant medication

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

Note: to satisfy inclusion criteria 8 and 9 the history of continuous treatment with high-dose ICS-LABA for at least 6 months prior to Visit 1 and use of OCS for at least 6 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

Oral corticosteroids

For eligibility purposes, all patients are required to be treated with oral corticosteroids for at least 6 months prior to Visit 1 and be on the stable maintenance dose of prednisone or prednisolone for at least 2 weeks prior to randomization. To aid the dose assessment, a guide for OCS dose equivalents is presented in Appendix H.

The dose of OCS will be titrated during optimization and reduction phases of the study (OCS optimization and reduction phases, for details see Sections 4.1.2 and 4.2.2). Patients who have 1 or more documented OCS reduction failures as outlined in Section 3.1, which defines the optimized dose prior to Visit 1, are not required to proceed through the pre-randomization optimization phase.

Oral corticosteroid 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.

Inhaled corticosteroid/long-acting β_2 agonist and other asthma controllers

All patients are required to be treated with high-dose ICS (>500 µg fluticasone dry powder formulation equivalents) and LABA for at least 6 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 electronic case report form (eCRF).

Inhaled corticosteroid/long-acting β_2 agonist 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 11) will be provided by AstraZeneca.

3.5.1.2 Rescue medication

Salbutamol, albuterol, and racemic preparations of albuterol (ie, levalbuterol) will be used as rescue medication during the study in the event of a worsening of asthma symptoms. 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 ß$_2$ agonists (SABA)**

Prophylactic use of SABA in the absence of symptoms (eg, prior to planned exercise), if deemed necessary by the patient and Investigator, 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.

Short-acting ß$_2$ agonist medication 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 nebulization, outside of managing an acute asthma exacerbation event, is discouraged unless the Investigator deems access to nebulized SABA essential for that patient. Occasions where SABA was administered via nebulization 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, Symbicort Maintenance and Reliever Treatment) 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 enrolment aside from oral corticosteroids, should be continued unchanged throughout the run-in and treatment period. Please refer to Section 3.1, inclusion criterion 11 for examples of allowed additional controller therapies for this study.

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 medical notes along with rationale 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-dose spirometry assessments will be performed at the study center at scheduled visits (see Table 1 and Table 2); restrictions to patient's background medication are required prior to the spirometry as described below (also see Section 5.1.3):

Visits 2-14: Patients will be asked to withhold their usual ICS/LABA medications on the mornings of scheduled spirometry visits. 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. 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.

For Visits 2-5, the patient's usual asthma medications may be administered following completion of the screening lung function procedures. For Visits 6-14, 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 5.1.3.

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

If the patient has taken rescue SABA within 6 hours of the planned spirometry assessment, they should ideally either

- remain at the center until such time that the 6-hour withholding time has been reached if it does not exceed the 1.5-hour spirometry window or
- 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 performed at least 6 hours after the last dose of SABA rescue medication.

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

Asthma medication restrictions on unscheduled (UNS) 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 UNS spirometry should be noted in the patient's record

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

The patients should be instructed not to take their usual asthma controller medication (ie, LABA) prior to a scheduled ECG assessment. Use of SABA should be avoided within 6 hours before ECG assessments. The medication restriction is waived for the screening ECG at 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 22 for examples and further details.

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

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

(d) When enrolling a patient who is on theophylline or digoxin, 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)

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

3.5.2.3 Other restrictions

(a) Fertile and sexually active patients or their partners should use highly effective contraceptive methods throughout the study and at least for 16 weeks (5 half-lives)

after last administration of the IP. Male patients should refrain from fathering child or donating sperm from the time of informed consent 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 and plasma from the time of informed consent and for 16 weeks (5 half-lives) after last dose of IP.

3.6 Discontinuation from investigational product

Patients will be discontinued from IP in the following situations:

1. Patient decision. The patient is at any time free to discontinue treatment without prejudice to further treatment

2. AE that, in the opinion of the Investigator, contraindicates further dosing

3. Risk to patient as judged by the Investigator or AstraZeneca

4. Severe noncompliance to Clinical Study Protocol (CSP)

5. Eligibility requirement found not to be fulfilled

6. Pregnancy

7. Lost to follow-up[1]

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 are missed or more than 2 scheduled doses of IP are missed during course of the study,

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

All patients who prematurely discontinue IP should return to the study center and complete the procedures described for the Premature IP Discontinuation visit (IPD) within 4 weeks (+7days) after last IP administration. The reason for premature discontinuation of IP should be documented in the source documentation and recorded in the eCRF.

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

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

at monthly intervals in order to collect AEs/SAEs, changes in concomitant medication and asthma exacerbation information. Patients not willing to continue to participate in the study should return to the study center 1 last time at 12 weeks (±3 days) after the last dose of IP for final study-related assessments.

3.7 Withdrawal from the study

3.7.1 Screen failures

Screen 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 as 'Incorrect Enrolment' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

3.7.2 Withdrawal 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 eosinophil ≥150 to <300/μL stratum will be closed to patients when the total number of adult patients in the stratum reaches approximately 60

2. The eosinophil ≥300/μL stratum will be closed to patients when the total number of patients in the stratum reaches approximately 150

The whole study will be closed for recruitment when the total number of patients reaches approximately 210.

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 will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow up AEs outside of the clinical study. The patient will return electronic patient reported outcome (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 center and complete procedures described for the IPD within 4 weeks (+7 days) after last dose of IP and Follow-up visit 12 weeks ±3 days after last dose of IP for final study-related assessments.

3.8 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

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

The Principal Investigator:

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

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

4. STUDY PLAN AND PROCEDURES

Table 1 Study plan – Enrolment, run-in/optimization phase; Visit 1 to Visit 6 (28-76 days)

Assessment/ activity	Refer to	Enrolment	Run-in/OCS optimization phase			
		V1 (w–10)	V2 (w–8)	V3 (w-6)	V4 (w-4)	V5 (w-2)
		Visit window (days)				
		0	+3	±3	±3	±3
Informed consent[a]	10.4	X				
Inclusion/exclusion criteria	3.1/3.2	X	X	X	X	X
Medical and asthma history	4.1.1	X				
Complete physical examination	5.2.1.1	X				
Brief physical examination	5.2.1.2		X	X	X	X
Weight, Height	5.3.1	X				
Vital Signs	5.2.2	X	X	X	X	X
ECG	5.2.3	X				
Local laboratory eosinophil test	5.3.3.1	X				
Blood concentration for theophylline and digoxin [b]	5.2.4	X				
Serum chemistry	5.2.4	X				
Hematology	5.2.4	X				
Urinalysis	5.2.4	X				
Serology (hepatitis B, C; HIV-1; HIV-2)	5.3.3.2	X				
Serum pregnancy test	5.2.4.1	X				

Table 1 Study plan – Enrolment, run-in/optimization phase; Visit 1 to Visit 6 (28-76 days)

Assessment/ activity	Refer to	Enrolment	Run-in/OCS optimization phase			
		V1 (w–10)	V2 (w–8)	V3 (w-6)	V4 (w-4)	V5 (w-2)
		Visit window (days)				
		0	+3	±3	±3	±3
FSH[c]	5.2.4.1	X				
PEF adherence check	5.1.4		X	X	X	X
Asthma Daily Diary adherence check	5.3.2.1		X	X	X	X
ACQ-6 completion on site	5.3.2.2	X				
ACQ-6 adherence check	5.3.2.2		X	X	X	X
AQLQ(S)+12 completion on site	5.3.2.3	X				
AQLQ(S)+12 adherence check	5.3.2.3		X	X	X	X
Screening pre-BD spirometry[d]	5.1.3	X	X	X	X	X
Screening post-BD spirometry[d,e]	5.1.3	X	X	X		
Assessment of asthma exacerbations	5.1.2		X	X	X	X
OCS dose reduction [f]	5.1.1.1		X	X	X	
OCS dose increase, if indicated [g]	5.1.1.1					X
Adverse events	7.1	X	X	X	X	X
Concomitant medication	3.5	X	X	X	X	X

a ICF can be signed 3 days prior to Visit 1
b If and when appropriate prior to randomization; for patients who are on theophylline or digoxin, (see Section 3.5.2.2 [d])
c FSH test done only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 month
d If patients do not demonstrate airway reversibility at either Visit 1 or Visit 2 and this is needed to qualify the patient for randomization, the site should reiterate the need to withhold short- and long-acting bronchodilators as required in Section 5.1.3 prior to Visit 3 in an effort to meet this inclusion criterion.

e The screening post-BD FEV_1 is not part of eligibility criterion for randomization for patients who have documented historical reversibility or methacholine sensitivity, as outlined in Section 3.1. The post-BD FEV_1; however, still needs to be completed as a baseline characteristic and should be performed using the guidance in Section 5.1.3.

f If the patient's OCS dose was optimized prior to Visit 5, the patient must be maintained on the optimized dose for at least 2 weeks and then can be randomized

g If the patient fails to meet titration criteria at Visits 3-4, the OCS dose should be returned to 1 level higher and Visit 5 can be activated on the same day.

ACQ-6 Asthma Control Questionnaire 6; AQLQ(S)+12 Standardized Asthma Quality of Life Questionnaire for 12 Years and Older; BD Bronchodilator; D Days; ECG Electrocardiogram; FEV_1 Forced expiratory volume in 1 second; FSH Follicle stimulating hormone; HIV Human immunodeficiency virus; ICF Informed consent form; OCS Oral corticosteroid; PEF Peak expiratory flow; V Visit; UNS Unscheduled; W Week.

Table 2 Study plan – Treatment phase and follow-up

Assessment/ activity	Refer to	Induction phase		Reduction phase						Maintenance phase	Follow-up	IPD	UNS[f]
		V6 (w0)R	V7 (w2)	V8 (w4)	V9 (w8)	V10 (w12)	V11 (w16)	V12 (w20)	V13 (w24)	V14 (w28) EOT	V15 (w36)		
		Visit window (days)[a]											
		±0	±3	±3	±3	±3	±3	±3	±3	+7	±3	+7	
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				
Vital Signs	5.2.2	X	X	X	X	X	X	X	X	X		X	X
ECG	5.2.3	X								X		X	
Serum chemistry[b]	5.2.4	X				X				X		X	
Hematology	5.2.4	X				X			X	X	X	X	
Urinalysis	5.2.4	X				X				X		X	

Table 2 Study plan – Treatment phase and follow-up

Assessment/ activity	Refer to	Induction phase		Reduction phase						Maintenance phase	Follow-up	IPD	UNS[f]
		V6 (w0)R	V7 (w2)	V8 (w4)	V9 (w8)	V10 (w12)	V11 (w16)	V12 (w20)	V13 (w24)	V14 (w28) EOT	V15 (w36)		
		Visit window (days)[a]											
		±0	±3	±3	±3	±3	±3	±3	±3	+7	±3	+7	
Urine pregnancy test (dipstick)[c]	5.2.4.1	X	X	X	X	X	X	X	X	X		X	
Total IgE	5.3.4	X											
Phadiatop	5.3.4	X											
PK	5.3.7	X		X	X	X	X		X	X	X	X	
ADA	5.3.9	X			X	X	X		X	X	X	X	
Serum biomarkers	5.3.8.1	X		X		X				X	X	X	
Sputum collection[d]	5.3.5	X				X				X	X	X	X
PEF adherence check	5.1.4	X	X	X	X	X	X	X	X	X		X	
Asthma Daily Diary adherence check	5.3.2.1	X	X	X	X	X	X	X	X	X		X	
ACQ-6 adherence check	5.3.2.2	X	X	X	X	X	X	X	X	X		X	
AQLQ(S)+12 adherence check	5.3.2.3	X	X	X	X	X	X	X	X	X		X	
Assessment of asthma exacerbations	5.1.2	X	X	X	X	X	X	X	X	X		X	X
OCS dose titration	5.1.1.1			X	X	X	X	X	X				X[g]

Table 2 Study plan – Treatment phase and follow-up

Assessment/ activity	Refer to	Induction phase		Reduction phase						Maintenance phase	Follow-up	IPD	UNS[f]
		V6 (w0)R	V7 (w2)	V8 (w4)	V9 (w8)	V10 (w12)	V11 (w16)	V12 (w20)	V13 (w24)	V14 (w28) EOT	V15 (w36)		
		Visit window (days)[a]											
		±0	±3	±3	±3	±3	±3	±3	±3	+7	±3	+7	
Pre-BD spirometry	5.1.3	X		X	X	X	X	X	X	X	X[d]	X	X
Post-BD spirometry for Sputum collection[d]	5.1.3	X				X				X	X	X	X
Body plethysmography[d]	5.3.6	X				X				X		X	
Randomization	4.2/6.5	X											
Administration of IP[e]	6.8	X		X	X	X	X	X	X				
Adverse events	7	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

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 5
c For WOCBP only, urine HCG test to be done at center on each treatment visit before any invasive procedures and IP administration
d The assessment is applicable for designated sites only. Post-BD spirometry as part of sputum induction procedure must be performed on site-owned devices.
e In case of anaphylaxis additional samples to be taken (see Section 6.9)
f Unscheduled visits may be initiated as needed, and additional assessments performed at these visits
g If unscheduled visit caused by exacerbation or infection (if applicable). Up titration only

ACQ-6 Asthma Control Questionnaire 6; ADA Anti-drug antibodies; AQLQ(S)+12 Standardized Asthma Quality of Life Questionnaire for 12 Years and Older; BD Bronchodilator; D Days; ECG Electrocardiogram; EOT End-of-treatment; FEV_1 Forced expiratory volume in 1 second; FU Follow-up; IP Investigational product; IPD IP discontinuation; OCS Oral corticosteroid; PEF Peak expiratory flow; PK Pharmacokinetics; R Randomization; V Visit; UNS Unscheduled; W Week.

4.1 Enrolment and run-in/optimization period

4.1.1 Enrolment (Visit 1)

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

In cases where the patient signs the informed consent form (ICF) prior to Visit 1, Visit 1 procedures must be initiated within 3 working days from the date of informed consent. Registration of the patient's enrolment via IWRS/IVRS should occur on day of Visit 1.

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. From Visit 1 until Visit 2, the baseline for the electronic patient-reported outcome (ePRO) parameters will be established.

A record of physician-diagnosed asthma, ICS-LABA and OCS use (Section 3.1, criteria 7, 8, and 9) and asthma exacerbations over the prior 12 months (Section 3.1, criterion 14) is required in 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 physician diagnosed asthma and prior asthma exacerbations can include clinic visit (primary or specialist healthcare provider [HCP]), emergency room or hospital records listing asthma as a current problem, plus documentation of at least 1 asthma exacerbation during the 12 months prior to signing the ICF.

A qualifying historical asthma exacerbation is a symptomatic worsening requiring use of systemic corticosteroids (ie, oral, intravenous [IV] or intramuscular [IM] in any healthcare setting) or a temporary increase from a stable maintenance dose of OCS, or that resulted in hospitalization.

Current, regular use of a high-dose ICS and LABA for at least 6 months prior to enrolment and OCS use for at least 6 continuous months prior to enrolment must be documented in the source. Inhaled corticosteroid and LABA may have been administered as either as fixed dose or 2 separate inhalers, and consistent with dose limits set by inclusion criterion 8. 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.

After confirmation of initial entry criteria 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). ACQ-6 and AQLQ(S)+12 should be completed during this visit.

Patients will continue on their current ICS/LABA and other controller(s) (if applicable) treatment with no changes. All patients must be on either prednisone or prednisolone as their OCS at Visit 1. If patients are on any other oral corticosteroids, they must agree to switch to an equivalent dose of the study-required prednisone/ prednisolone as their OCS for the duration of the study. Please refer to Appendix H for the OCS dose-equivalence guide.

Following registration of enrolment, screening procedures may begin to assess study eligibility (inclusion/exclusion) criteria (see Table 1).

4.1.2 Run-in/oral corticosteroid optimization phase (Visit 2 to Visit 5)

Pulmonary function tests and assessment of reversibility (maximum post-BD value of lung function) may be repeated at Visit 2 or Visit 3 if reversibility was not achieved at Visit 1 and this is needed to qualify the patient for randomization (see Section 5.1.3.1).

The run-in/OCS optimization phase will be a maximum of 8 weeks in duration (from Visit 2, Week -8 to Visit 6, Week 0). The patient should remain on their current ICS/LABA treatment with no changes throughout this period. Assessments applicable for the period are listed in Table 1.

Patients with documented failures of OCS reduction within 6 months prior to Visit 1 (refer to inclusion criterion 10) will not be required to proceed through the OCS optimization phase during the run-in period. For these patients, Visit 2 must be combined with Visit 5. The patient must be maintained on the same OCS dose until randomization at Visit 6. In such cases, all assessments listed in Table 1 for Visit 2 should be conducted at this visit. All eligibility criteria **mus**t be met prior to randomization at Visit 6.

Patients who do not have documented failures of OCS reduction within 6 months prior to Visit 1 (refer to inclusion criteria 10), will enter the OCS optimization phase. Their OCS dose will be titrated (see Section 5.1.1.1) to ensure they are taking the minimum effective OCS dose without losing asthma control.

The OCS dose titration must be initiated at Visit 2. The Investigator should follow the titration schedule list in Table 3. Visit 2 is the only titration visit that will not be based upon a protocol-captured set of baseline data, because the first baseline data capture period is not yet complete. The decision to initiate OCS dose reduction at Visit 2 is at the discretion of the Investigator and can include consideration of Visit 2 spirometry and data captured in the electronic diary compared with a historic baseline from the past 6 months. If inclusion criterion 13 has not been met and reversibility has not been demonstrated at Visit 1 or Visit 2, the patient must be brought back in for Visit 3, after initiation of OCS down titration at Visit 2, to demonstrate reversibility (as per inclusion criterion 13). The patient must be screen failed if they fail to demonstrate reversibility. All patients undergoing OCS down titration in the optimization phase must perform pre-BD spirometry at Visit 2 as this will form part of the assessment for OCS titration (Section 5.1.1.1) at subsequent visits in the run in/ optimization phase

If at Visit 2, the patient is judged not to be a candidate for OCS dose reduction based upon asthma symptoms or other clinical reasons in the opinion of the Investigator, he/she should be screen-failed.

At Visit 3 and Visit 4, the dose of OCS may be reduced only if all criteria listed in Section 5.1.1.1 are met. The reductions can occur at 2-week intervals according to the titration schedule (see Table 3). If a patient does not meet all criteria listed in Section 5.1.1.1, the OCS dose should be returned to at least the previous effective dose (ie, the higher dose level prior to the titration criterion not being met) and the visit must be combined with Visit 5. **Once the OCS dose is uptitrated, no further OCS dose reductions should be performed. The patient should be maintained on that OCS dose until randomization (Visit 6).**

At Visit 5, if the patient still meets all of the criteria for OCS dose down-titration, this patient must be screen-failed (refer to exclusion criterion 18). If the patient does not meet all criteria listed in Section 5.1.1.1, the OCS dose should be returned to at least the previous effective dose (ie, the higher dose level prior to the titration criterion not being met) and should be maintained on that OCS dose until randomization (Visit 6).

The optimized dose of OCS is defined as a lowest dose of OCS at which patient meets criteria listed in Section 5.1.1.1. In cases when the patient is optimized on their OCS dose prior to Visit 5 (Week-2), that visit should be combined with Visit 5 (eg, Visit 3 would be combined with Visit 5). He/she should be maintained at the optimized dose of OCS for at least 2 weeks and then can be randomized at Visit 6. Once the OCS dose has been uptitrated, no further OCS dose reduction should be performed. The optimized dose reached during the OCS optimization phase becomes the patient's baseline OCS dose for analysis purposes.

It is possible that the patient's asthma symptoms may worsen (excluding exacerbation and/or infection requiring antiviral or antibiotic therapy), in between visits, during the run in/optimization period, as evidenced through patient history and corroborated through the data collect through eDiary. In this case, the OCS dose can be increased to a previous effective dose without a visit to the clinic. The patient can be assessed in clinic at the earliest opportunity or at the next scheduled visit (at the Investigator's discretion). If the patient is assessed during an unscheduled visit, he/she should still return for the next scheduled visit. This scheduled visit can be combined with Visit 5. The patient should be maintained on this new OCS dose for at least 2 weeks prior to randomization (Visit 6).

If the patient experiences an asthma exacerbation requiring evaluation in an Urgent Care Center, in an Emergency Department (ED), Hospitalization, or temporary increase (bolus/burst) of systemic steroids, they do not need to be screen failed. The exacerbation should be treated according local standard of care. After completing the treatment for the exacerbation, the patient should return back to his/her regular maintenance dose of OCS. He/she must remain on this dose for 2 weeks and then return for Visit 5. The maintenance OCS dose must be at least 1 dose-level higher than the dose at which the exacerbation occurred. The patient should be maintained on this OCS dose for 2 weeks prior to randomization (Visit 6). The patient should continue to complete the eDiary daily during the

asthma exacerbation. This is important as compliance will be assessed as per inclusion criteria 18, 19, and 20.

If a patient reaches asthma control at an OCS dose of ≤5mg during the optimization phase, the patient will be a screen failure and will not be randomized (refer to exclusion criterion 17; at Visit 6, the OCS dose must be >5 mg). If the patient does not reach an optimized dose of the OCS by the end of the run-in/optimization phase, the patient should be screen failed and cannot be randomized.

The post-BD FEV_1 should be performed using the guidance in Section 5.1.3.1, if necessary. If inclusion criterion 13 was not met and reversibility has not been demonstrated at Visit 1 or Visit 2, the patient must be brought back in for Visit 3, after initiation of OCS down titration at Visit 2, to demonstrate reversibility. The patient must be screen failed if they fail to demonstrate reversibility. Those patients who have historical documentation of reversibility within 24 months prior to Visit 1, or documentation of airway hyperresponsiveness (PC_{20} FEV_1 methacholine concentration ≤8mg/ml within 12 months prior to planned date of randomization or documented FEV_1 variability of ≥20% between 2 consecutive clinic visits within 12 months prior to planned date of randomization must also perform pre-BD and post-BD spirometry as outlined in Section 5.1.3.1 to establish baseline characteristics.

Patient eligibility should be evaluated at each visit during the run-in/OCS optimization phase with the relevant documentation entered in the source and eCRF.

Patients whose compliance with the electronic diary is <70% will be given the option once during screening to reschedule a study visit (with the exception of Visit 6) within 72 hours.

Table 3 Oral corticosteroid titration schedule during the optimization phase (Visit 2 to Visit 5)

Enrolment Visit	**Run in/Optimization Phase (OCS dose in mg)**			
V1/W -10	**V2/W -8**	**V3[a]/W -6**	**V4[a]/W -4**	**V5/W -2**
40	35	30	25	A
37.5	32.5	27.5	22.5	A
35	30	25	20	A
32.5	27.5	22.5	17.5	A
30	25	20	15	A
27.5	22.5	17.5	12.5	A
25	20	15	10	A
22.5	17.5	12.5	7.5	A
20	15	10	7.5	A

Table 3 Oral corticosteroid titration schedule during the optimization phase (Visit 2 to Visit 5)

Enrolment Visit	Run in/Optimization Phase (OCS dose in mg)			
17.5	12.5	7.5	5	A & B
15	10	7.5	5	A & B
12.5	7.5	5	B	
10	7.5	5	B	
7.5	5	B		

[a] Check if the patient meets all the criteria listed in Section 5.1.1.1. If yes, then down titrate as per Table 3. If no, the OCS dose should be returned to at least the previous effective dose (ie, the higher dose level prior to the titration criterion not being met) and the visit must be combined with Visit 5 (eg, a patient met the criteria and was down titrated to 20 mg at Visit 3; at Visit 4, the patient does not meet the criteria for down titration; therefore, the patient must be uptitrated to at least 25mg).

A. At this visit, if the patient's symptoms are stable and the patient meets all of the criteria in Section 5.1.1.1 for further down titration, the patient must be screen failed (refer to exclusion criterion 18).

B. At this visit, if the patient's symptoms are stable and the patient meets all of the criteria in Section 5.1.1.1 for further down titration, the patient must be screen failed (refer to exclusion criterion 17).

4.1.3 Re-screening

Patients with respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the run-in/optimization phase may also be re-screened (exclusion criterion 6). They may be re-screened 30 days after recovery, eg, completion of the therapy.

Re-screening for the above mentioned reasons is allowed only once for the patient.

If the reason for screen failure was transient (including but not limited to study-supplied equipment failure or 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 approval for re-screening should be filed in the Investigator Study File (ISF).

Rescreening of patients for any other reason will be allowed only upon approval of the medical monitor or AstraZeneca Study Physician.

4.2 Randomized treatment period

The randomized treatment period is divided into 3 phases based on the OCS dose adjustment: induction phase (Section 4.2.1), reduction phase (Section 4.2.2), and maintenance phase (Section 4.2.3).

Inclusion criteria at randomization will be confirmed at Visit 6. Before randomization the patient's compliance with usual asthma controller ICS/LABA, OCS, and ePRO completion must be confirmed (see Section 3.1, inclusion criteria 18, 19, and 20).

Patients confirmed to be eligible will be randomized at Visit 6 (Week 0) in a 1:1:1 ratio to receive benralizumab 30 mg either every 4 weeks (Q4W) throughout the treatment period, or every 4 weeks for the first 3 doses and then every 8 weeks (Q8W) thereafter, or placebo Q4W.

The first dose of the IP will be administered at Visit 6 after the patient's randomization via IWRS/IVRS.

Following randomization, the patient will enter a 28-week double-blind treatment period, with the last dose of benralizumab/placebo administered at Visit 13 (Week 24).

At Week 2 (Visit 7), the patient will be seen at the study center for a health check; IP will not be administered at this visit. Procedures specific for this visit are listed in Table 2.

Starting at Visit 8, patients will have scheduled visits at 4-week intervals to complete protocol-specific assessments and IP administration, as listed in Table 2. Restrictions as set out in Section 3.5.2 will continue to apply throughout the treatment period.

Patients will continue to monitor lung function at home, as well as record asthma symptoms and responses to questionnaires using the ePRO device throughout the 28-week treatment period (see Section 5.3.2 for details).

At Week 28, patients will come to the center for the EOT visit.

All patients who prematurely discontinue IP should return to the study center and complete the procedures described for the Premature IP Discontinuation visit (IPD) within 4 weeks (+7days). 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 at monthly intervals in order to collect AEs/SAEs, changes in concomitant medication, health care utilization, and asthma exacerbation information. Patients not willing to continue to participate in the study should return to the study center 1 last time at 12 weeks (±3 days) after the last dose of IP for final study-related assessments.

Patients will return the ePRO device at the EOT (or IPD, if applicable) visit.

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

4.2.1 Induction phase

The induction phase will start at Week 0 (Visit 6) and will continue until Week 4 (Visit 8). During this time, patients will remain on all of their regular asthma controller medications. No dose adjustments to OCS will be made during this period; patients will continue the optimized OCS dose that was achieved during OCS optimization phase. The pre BD

spirometry of acceptable quality must be performed at Visit 6. The pre-BD spirometry will form part of the assessment for OCS titration (Section 5.1.1.1) at subsequent post randomization visits until Visit 13.

4.2.2 Reduction phase

The reduction phase will start at Week 4 (Visit 8) and will be completed at Week 24 (Visit 13). The first reduction of OCS dose should occur at the Week 4 visit (Visit 8). Visit 8 is the only titration visit in the reduction phase that will not be based upon a protocol-captured set of baseline data as the patient is already on an optimized OCS dose. At all other visits in the reduction phase, the OCS dose reduction must take place only when all the titration criteria are met as per Section 5.1.1.1. If Visits 9, 10, 11, 12, and 13, the patient does not meet all criteria listed in Section 5.1.1.1, the OCS dose should be returned to at least the previous effective dose (ie, the higher dose level prior to the titration criterion not being met). Oral corticosteroid dose reductions can occur at 4-week intervals according to the titration schedule of OCS dose reductions presented in Table 4. **Once the OCS dose has been uptitrated, no further OCS dose reduction should be performed. This dose should be maintained until the EOT (Visit 14).** The occurrence of exacerbations, changes in symptoms, and rescue medication use will be assessed.

Table 4 Oral corticosteroid dose titration schedule during the reduction phase (Visit 8 to Visit 13) [a, b]

Optimized dose at V6	V8/W4	V9/W8	V10/W12	V11/W16	V12/W20	V13/W24
40	35	30	25	20	15	10
37.5	32.5	27.5	22.5	17.5	12.5	7.5
35	30	25	20	15	10	7.5
32.5	27.5	22.5	17.5	12.5	7.5	5
30	25	20	15	10	7.5	5
27.5	22.5	17.5	12.5	7.5	5	5
25	20	15	10	7.5	5	5
22.5	17.5	12.5	7.5	5	5	5
20	15	10	7.5	5	5	5
17.5	12.5	7.5	5	5	5	2.5
15	10	7.5	5	5	2.5	1.25
12.5	7.5	5	2.5	1.25	0	0
10	7.5	5	2.5	1.25	0	0
7.5	5	2.5	1.25	0	0	0

[a] All doses expressed in mg/day
[b] A daily dose of 1.25 mg may be administered as 2.5 mg every other day

Patients who experience an asthma exacerbation requiring evaluation in an Urgent Care Center, in ED, Hospitalization, or temporary increase of systemic steroids (bolus/burst dosing) should be returned to the previous effective OCS dose (ie, the higher dose level prior to the titration criterion not being met) after they have returned to their baseline level of asthma control. This dose should be maintained until the EOT (Visit 14).

NOTE: OCS dose reduction may take place only when criteria for OCS dose reduction are met (not applicable for Visit 8, see Section 5.1.1.1).

4.2.3 Maintenance phase

Patients will be maintained for the 4-week period after Week 24 to Week 28 on the stable dose of OCS achieved during the reduction phase, or if requirement for OCS was eliminated, then maintained without OCS. Patients will be maintained without further OCS dose adjustments until their last visit within the study to assess symptoms, ACQ-6, and exacerbations. Patients who remain on IP for the double-blind treatment period as defined in the protocol (see Section 1.5) may be eligible to enrol in the follow-on extension study (these patients will not attend the Follow-up visit at Week 36).

4.3 Follow-up period

Patients who have remained on IP for the double-blind treatment period as defined in the protocol (see Section 1.5) may be eligible to enrol in the follow-on extension study

Patients who complete Week 28 (Visit 14) and do not enter the follow-on extension study will be requested to return to the study center at Week 36 for the follow-up assessments. During these visits, patients will be assessed for any ongoing safety issues, and any potential prospective AEs; serum biomarker, PK, and immunogenicity samples will be collected (see Table 2).

5. STUDY ASSESSMENTS AND PROCEDURES

5.1 Efficacy assessments

5.1.1 Assessment of oral corticosteroid dose

During run-in/OCS optimization phase, the minimum OCS dose while maintaining asthma control will be reached for each patient. The optimized dose will be considered as the baseline OCS dose.

The baseline OCS dose will be maintained at the same level from Visit 6 to Visit 8 (induction phase).

The reduction of the OCS dose will commence at Visit 8 and will continue at 4-week intervals until Visit 13 in accordance with OCS dose titration schedule provided in Table 4 (reduction phase). During reduction phase, a minimum stable OCS dose, or complete elimination of requirement for OCS, while maintaining asthma control, will be reached for each patient.

If a patient does not meet titration criteria, the OCS dose should be returned to the previous effective dose (ie, the higher dose level prior to the titration criterion not being met) and should be maintained on that OCS dose until EOT (Visit 14).

No adjustments will be made to OCS dose after Visit 13 and the patient will enter the maintenance phase.

The OCS dose changes will be documented in the source documentation and recorded in the appropriate eCRF form.

Patient should have a minimum of 70% compliance with ePRO completion between each study visit (from Visit 6 to Visit 14) based on Asthma Daily Diary for OCS dose titration. If compliance falls under 70%, OCS dose titration may be performed at the Investigator's discretion according to the protocol-specified titration criteria.

5.1.1.1 Oral corticosteroid dose titration

Oral corticosteroid dose titration occurs during the Optimization Phase (Table 3) and again during the Reduction Phase (Table 4).

For the optimization phase, the baseline will be the mean of measures (morning PEFs, SABA use, night time awakenings, and total asthma symptom score) collected on each day between Visit 1 and Visit 2. Dose titration begins at Visit 2 at the discretion of the Investigator (refer to Section 4.1.2). Baseline FEV_1 for the optimization phase will be collected at Visit 2.

For the dose reduction phase, the baseline will be the mean of measures (morning PEFs, SABA use, night time awakenings, and total asthma symptom score) collected on each day between Visit 5 and Visit 6. Dose titration begins at Visit 8 and it is the only titration visit in the reduction phase that will not be based upon a protocol-captured set of baseline data as the patient is already on an optimized OCS dose. Baseline FEV_1 for dose reduction phase will be collected at Visit 6.

Patients who meet all of the following criteria are eligible for OCS dose reduction during the optimization phase (Table 3) and during the reduction phase (Table 4):

- Pre-BD FEV_1 ≥80% of baseline
- Morning PEF ≥80% of mean morning measures over the 14 days period prior to the scheduled study visit as compared with baseline
- Mean night time awakenings ≤50% increase over the 14 days period prior to the scheduled study visit, as compared with baseline
- SABA rescue medication use of not more than 4 inhalations/day above the mean value over 14 days period prior to the scheduled study visit, as compared with baseline, or above 12 inhalations/day
- No requirement to increase the dose of OCS for asthma symptoms since the last visit

During the optimization phase, if the patient fails to meet all of the above criteria at Visit 3, further reduction of the OCS dose will be stopped and the patient will be returned to an OCS dose that is at least 1 dose level higher than the OCS dose at which further titration criteria was not met. If randomized at Visit 6, the patient will then be maintained at this OCS dose until the reduction phase (Visit 8).

At Visit 8, the down titration will be initiated. If, at any subsequent visits during the reduction phase, the patient fails to continue to meet the criteria for down titration, further reduction of the OCS dose will be stopped and the patient will be returned to an OCS dose that is at least 1 dose level higher than the OCS dose at which the down titration criteria were not met. Once the OCS has been uptitrated, no further OCS dose reduction should be performed.

During the post-randomization phase, not all patients will be allowed to reduce their OCS dose to 0. A minimum maintenance dose will be required for patients whose dose at Visit 6 is 15 – 40 mg/day (Table 4); these patients may not be reduced to doses lower than that which is specified.

If, in the opinion of the Investigator, additional OCS dose reductions are not clinically indicated (due to disease factors that may affect patient safety), titration may be stopped after discussion with the AstraZeneca Study Physician. The patient should be returned to a dose at least 1 level higher (unless a temporary bolus/burst of steroid is warranted) and no further reductions may take place. In these instances, the reason(s) for stopping the OCS dose reductions must be documented in the source notes.

For statistical analysis purposes, in the event that titration is terminated prior to Visit 13, a patient's final OCS dose will be recorded as 1 dose level higher than that which directly preceded termination.

The titration schedule of OCS dose reduction during the reduction phase is presented in Table 4.

5.1.2 Assessment of asthma exacerbations

The treatment, including changes in the OCS dose and duration and the use of additional, potentially emergent therapies is at the discretion of the treating physician. For the purpose of the CSP, an asthma exacerbation will be defined as a worsening of asthma that leads to any of the following:

- A temporary bolus/burst of systemic corticosteroids (at a dose at least 1 level higher than the current titration step for at least 3 days to treat symptoms of asthma worsening,
- an emergency room visit due to asthma that required systemic corticosteroids, or
- an inpatient hospitalization due to asthma.

Discontinuation due to exacerbation after Visit 6 (the OCS dose reduction period) is not mandatory. Those who experience an exacerbation after randomization may remain on IP at

the Principal Investigator's discretion. Following resolution of the exacerbation, the patient should be placed on the OCS dose 1 step higher than that which they were on when the exacerbation occurred (see Table 4).

Up titration of OCS dose during optimization to 1 level higher is not considered an exacerbation

Worsening of asthma is defined as new or increased symptoms and/or signs (eg, examination or lung function) that can be either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (ie, diary-driven).

The baseline during the optimization phase will be the mean of measures collected each day between Visit 1 and Visit 2.

For the dose reduction phase, the baseline will be the mean of measures collected on each day between visit 5 and visit 6.

The ePRO device will be programmed to alert both the patient and study center when certain pre-specified worsening thresholds are crossed including:

- Decrease in morning peak flow ≥20% on at least 2 consecutive days compared with baseline, and/or
- An increase in rescue medication use of 4 or more puffs, or use of 1 new or additional nebulized β_2 agonist on at least 2 consecutive days compared with the average use during baseline, and/or
- An increase of 2 nocturnal awakenings due to asthma over a 7-day period compared with the average during baseline, 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 baseline average or the highest possible score [daily score of 6]), on at least 2 consecutive 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 within ≤7 days of the last dose of systemic steroids 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. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study centers (eg, by the primary care HCP or at an ED/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.

5.1.3 Spirometry

During the run in /optimization phase, all patients must perform pre-BD and post-BD spirometry. Assessment of reversibility may be repeated at Visit 2 or Visit 3 if reversibility was not achieved at Visit 1 (refer to Section 5.1.3.1)

Those patients who have historical documentation of reversibility within 24 months prior to Visit 1, or documentation of airway hyperresponsiveness (PC_{20} FEV_1 methacholine concentration ≤8mg/ml within 12 months prior to planned date of randomization or documented FEV_1 variability of ≥20% between 2 consecutive clinic visits within 12 months prior to the planned date of randomization must also perform pre-BD and post-BD spirometry as outlined in Section 5.1.3.1 to establish baseline characteristics. Nevertheless, their historical data will be used to meet eligibility prior to randomization as per inclusion criterion 13.

All patients undergoing OCS down titration in the optimization phase must perform pre-BD spirometry at Visit 2 as this will form part of the assessment for OCS titration (Section 5.1.1.1) at subsequent visits in the run in/ optimization phase.

For the reduction phase, pre-BD FEV_1 must be performed at Visit 6 and will form part of the assessment for OCS titration (Section 5.1.1.1) at subsequent visits.

General requirements

Lung function (FEV_1 and forced vital capacity [FVC]) at the study center will be measured by spirometry using equipment provided by a 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 center personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate spirometry procedures manual.

Important! Patients should be instructed to restrict the use of their usual ICS/LABA medication prior to scheduled center visit spirometry as this will affect the pre-BD FEV_1 value that may be taken subsequently at the center. Twice daily ICS and LABA therapies should be withheld for 12 to 24 hours; once daily therapies containing ICS, LABA, or LAMA therapies should be withheld for ≥24 hours for eligibility assessment. **For the same reason, patients should not use their rescue SABA medication (albuterol/salbutamol) within 6 hours of a scheduled center visit spirometry.** This restriction is particularly critical for efficacy measures taken during the treatment period, but should also facilitate meeting the screening FEV_1 and reversibility eligibility criteria.

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

For reaching the end-expiratory level, the following 2 criteria must be complied with according to ATS/ERS:

- Duration of expiration
  - Patients must exhale for at least 6 seconds.
- End of Test Criteria
  - Towards the end of the expiration, it is important to motivate the patient to try hard. Within the last second of expiration the exhaled volume must not exceed 25 mL.

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

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each center spirometry session and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded. The best efforts will be based on the highest FEV_1. The absolute measurement (for FEV_1 and FVC), and the percentage of predicted normal (PN) 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

The post-BD spirometry procedures should commence within 30±15 minutes after pre-bronchodilator (pre-BD) spirometry according to the regimen for reversibility testing outlined in Section 5.1.3.1.

Post-bronchodilator (post-BD) spirometry will also be performed in a subset of patients who participate in the sputum assessment, as part of the sputum induction procedure on site-owned spirometry devices.

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

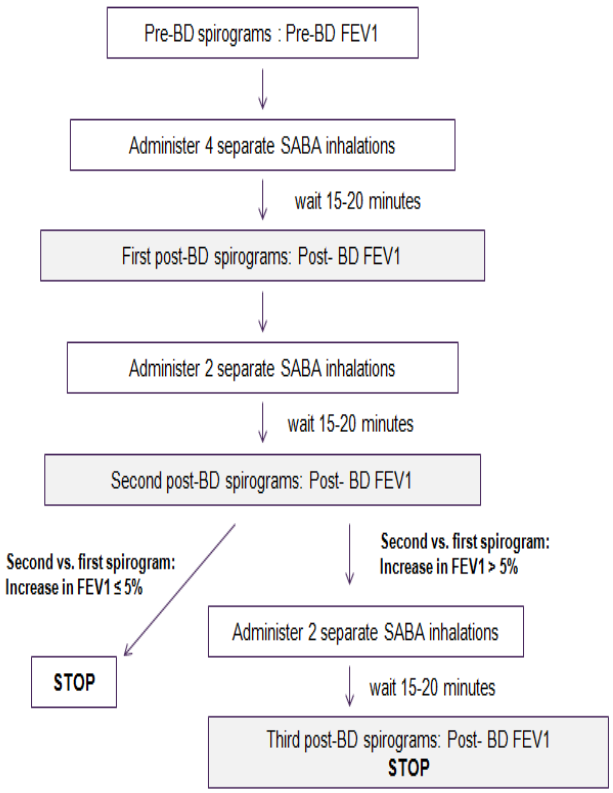
The patient's asthma morning asthma controller therapy must not be given until after the initial pre-BD spirometry is complete; asthma controller medications may be given after final post-BD spirometry assessments. Investigational product dosing should also be withheld until pre-BD spirometry is complete.

Detailed sputum collection procedures, including related pre and post-BD spirometry measurements are available in a separate sputum manual provided to the designated study centers.

5.1.3.1 Reversibility test and post-bronchodilator FEV_1 assessment

The procedure described in this section refers to the reversibility testing at Visit 1 or Visit 2 or Visit 3 (to evaluate inclusion criterion 13, if applicable). Bronchodilatation can be induced using albuterol (90 µg metered dose), salbutamol (100 µg metered dose), or levalbuterol (45 µg metered dose) up to a maximum of 8 inhalations). It is highly recommended to use a spacer device for this procedure. The algorithm for reversibility testing is outlined in Figure 2.

Figure 2 Reversibility testing algorithm



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

2 After a gentle and complete expiration, albuterol, salbutamol or levalbuterol is inhaled in 1 breath to total lung capacity (TLC) from a spacer device. The breath is then held for 5–10 seconds before the patient exhales. Four separate inhalations are delivered at approximately 30- second intervals. Post-BD spirometry should be performed 15-20 minutes later.

3 If the patient has not met reversibility criteria (and needs to do so to meet inclusion criterion 13), an additional 2 inhalations of albuterol, salbutamol, or levalbuterol can be administered as single inhalations, 30 seconds apart (for a total of 6 inhalations). A second post-BD spirometry should be performed 15-20 minutes later.

4 If the patient still has not met reversibility criteria (and needs to do so to meet inclusion criterion 13), an additional 2 inhalations can be administered (for a total of 8 inhalations). A third 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 reversibility testing at Visit 1, Visit 2, or Visit 3, it is acceptable to stop the procedure when eligibility criterion is met.

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

Reversibility is calculated as follows:

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

Record keeping

A signed and dated copy of the pre- and post- BD printout must be kept at study center 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 (GINA 2014).

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

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

5.1.4 Home lung function testing

An electronic, hand-held spirometer (peak flow meter) will be dispensed to the patient on Visit 1.

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 1 (Week -10) until the morning of Visit 14 (Week 28) using the provided 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.

The Investigator/authorized delegate will check the patient's adherence to correct use of the peak flow meter at each visit as shown in Table 1 and Table 2 (or at EOT Visit if prematurely discontinued from the study).

5.2 Safety assessments

5.2.1 Physical examination

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

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

5.2.1.1 Complete physical examination

The complete physical examination 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, and cardiovascular and respiratory systems. For the brief physical examination only information on whether the assessment was performed or not is to be recorded.

5.2.2 Vital signs

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

The vital signs will be taken prior to blood drawing, IP administration, and, if possible, usual asthma controller medication. Vital signs should also be taken prior to per protocol BD administration if applicable for that visit.

Pulse rate and blood pressure (BP) 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 BP.

Respiration rate will be obtained after the 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 degrees Celsius before IP administration in accordance with local standards.

5.2.3 Electrocardiogram

Electrocardiograms will be performed in accordance with the schedules provided in Table 1 and Table 2.

The assessments will be performed prior to blood drawing, spirometry, IP administration, and BD administration.

A 12-lead ECG will be taken in supine position, after the patient has been resting for at least 5 minutes. The assessment should be performed before interventions with the patient (eg, spirometry and administration of asthma-related medications and IP).

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.

Electrocardiogram data and evaluation will be recorded in the eCRF.

For all patients, the printouts of the ECG will be collected, signed, dated, and stored at the study center 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 5) 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.

Hematology and urinalysis will be assessed in line with the schedules provided in the in Table 1 and Table 2; a detailed schedule of the chemistry tests is presented in Table 6.

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 AE 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 center.

Table 5 List of safety laboratory tests

Serum chemistry		**Hematology**	**Urinalysis**
Alkaline phosphatase	Gamma-GT (gamma-glutamyl transpeptidase)	Hematocrit	Appearance
ALT (alanine aminotransferase)	Glucose	Hemoglobin	Blood
AST (aspartate aminotransferase)	Phosphorus	Mean corpuscular volume (MCV)	Colour
BUN (blood urea nitrogen)	Potassium	Platelet count	Glucose
Calcium	Sodium	Red blood cell (RBC) count	Ketones
Chloride	Total bilirubin	WBC count with differential[a]	Microscopy including WBC/high power field (HPF), RBC/HPF
CO_2 (carbon dioxide)	Total cholesterol		pH
Creatinine	Uric acid		Specific gravity
Serum concentration[b]			

a eosinophil, basophil and monocyte counts will be redacted from the central laboratory reports, except Visit 1 laboratory report (see Section 6.6).

[b] If and when appropriate prior to randomization; For patients who are on theophylline and digoxin (see Section 3.5.2.2 [d])

Table 6 Schedule of serum chemistry tests

VISIT	V1	V6	V10	V14	IPD
Alkaline phosphatase	X	X	X	X	X
ALT	X	X	X	X	X
AST	X	X	X	X	X
BUN	X	X	X	X	X
Calcium, serum	X			X	X
Chloride, serum	X			X	X
CO_2 (carbon dioxide)	X			X	X
Creatinine	X	X	X	X	X
Gamma-GT	X	X	X	X	X
Glucose	X			X	X
Phosphorus, serum	X			X	X
Potassium, serum	X			X	X
Sodium, serum	X			X	X
Total bilirubin	X	X	X	X	X
Total cholesterol	X			X	X
Uric acid	X			X	X

IPD Premature investigational product discontinuation

5.2.4.1 Pregnancy Test

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

- Serum beta-HCG (Beta- human chorionic gonadotropin): To be done at screening Visit 1 only, for WOCBP (analyzed at central laboratory)
- FSH: To be done at screening Visit 1 only, for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 month
- Urine HCG: To be performed at the study center for WOCBP at each treatment visit before any invasive study procedures (eg, blood sampling, spirometry) and IP administration using a dipstick. A positive urine test result must be confirmed with serum beta HCG.

5.3 Other assessments and procedures

5.3.1 Weight and height

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

Note: Weigh and height will be taken on screening Visit 1 only.

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 1. The study center 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 1 to the morning of Visit 14. 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 (ICS/LABA and OCS). There will be triggers in the ePRO device to alert the patients to signs of worsening of asthma and to contact their physician (refer to Section 5.1.2).

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

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

Home lung function measurement

For details regarding home lung function measurement please refer to Section 5.1.4.

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 1 to Visit 14.

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

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 (ICS/LABA) will be recorded in the Asthma Daily Diary in the morning and evening as "yes" or "no", whereas OCS will be recorded in the evening as "yes", "no, dose was missed", not scheduled today" or "not applicable, dose reduced to 0".

5.3.2.2 Asthma Control Questionnaire

The Asthma Control Questionnaire (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 β_2 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 $\leq$0.75 indicate well-controlled asthma, scores between 0.75 and $\leq$1.5 indicate partly controlled asthma, and a score >1.5 indicates not well controlled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered to be clinically meaningful.

The questionnaire will be completed using the ePRO device.

The ACQ-6 will be completed by the patient on the ePRO device at Visit 1 and the patient will be given the device to take home.

After Visit 1, the patient will complete the ACQ-6 at home every 7 days (±1 day) until Visit 6 or Randomization (Week 0). The patient will bring the device to the randomization visit and complete the ACQ-6 on site during the randomization visit (Week 0).

After randomization, the patient will complete the ACQ-6 at home every 2 weeks (±1 day) until Visit 14 (Week 28), where the ACQ-6 will be completed by the patient during study visit at site.

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 Standardized Asthma Quality of Life Questionnaire for 12 years and older

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

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

Patients are asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The 4 individual domain scores (symptoms, activity limitations, emotional function, and environmental stimuli) are the means of the responses to the questions in each of the domains. Individual improvement in both the overall score and individual domain scores of 0.5 has been identified as a minimally important change, with score changes of >1.5 identified as large meaningful changes

The questionnaire will be completed using the ePRO device.

The AQLQ(s)+12 will be completed by the patient on the ePRO device at Visit 1 and the patient will be given the device to take home.

After Visit 1, the patient will complete the AQLQ(s)+12 at home every 2 weeks (±1 day) until Visit 6 or Randomization (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).

After randomization, the patient will complete the AQLQ(s)+12 at home every 4 weeks (±1 day) until Visit 14 (Week 28) where the AQLQ(s)+12 will be completed by the patient during study visit at site.

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

5.3.3 Other assessments

5.3.3.1 Local laboratory eosinophil test

Only patients with an absolute blood eosinophil count of ≥150 cells/μL at Visit 1, as assessed at the local laboratory, will be eligible for randomization (see inclusion criterion 6).

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

5.3.3.2 Serology

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

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

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

5.3.4 Total IgE and Phadiatop

The test will be performed at Visit 6 (Week 0, see Table 2). Analysis will be performed by the central laboratory.

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

5.3.5 Sputum collection

Sputum will be collected to evaluate sputum total cell and differential cell counts and to assess the levels of biomarkers associated with asthma, inflammation, eosinophil progenitor cells by flow cytometry, the pharmacology of benralizumab, and eosinophil recruitment, activation, and survival.

The sputum assessment will be conducted at designated sites with the aim of obtaining samples from approximately 60 patients.

Details related to sputum induction, collection, and processing are available in separate manual provided to the designated study centers.

The sputum will be induced by inhaling hypertonic saline.

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

The samples will be analyzed by a central laboratory on behalf of AstraZeneca. AstraZeneca or a designee will retain sputum 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, including sputum biomarkers will not be reported in the CSR, but in separate reports and in scientific publications as appropriate.

5.3.6 Body plethysmography

Body plethysmography is to be performed only by sites participating in the sputum collection and will be performed on approximately 60 patients who agree to provide sputum for study purposes.

Lung volume subdivisions which include total lung capacity (TLC), residual volume (RV), vital capacity (VC), functional residual capacity (FRC), and inspiratory capacity (IC) will be performed at study sites by the Investigator or qualified designee according to ATS/ERS guidelines (Wanger et al 2005) according to the study schedule (see Table 2). Lung volumes will be determined by body plethysmography. The test will be performed by qualified pulmonary function technicians with experience performing this assessment. At least 3 FRC values that agree within 5% (ie, the difference between the highest and lowest value divided by the mean is <0.05) should be obtained and the mean value reported. Measurements using the body plethysmography will be conducted at visit 6, 10 and 14. Prior to the assessment, certain restrictions need to be adhered to. Twice daily ICS and LABA therapies should be withheld for 12 to 24 hours; once daily therapies containing ICS, LABA, or LAMA therapies should be withheld for ≥24 hours to scheduled assessment. Patients should also not use their rescue SABA medication (albuterol/salbutamol) within 6 hours of a scheduled assessment. This assessment is to be performed on all subjects enrolled for sputum collection. Each site will be allowed to use their own body boxes to conduct assessments provided they meet the quality and experience criteria set by AstraZeneca. Details related to this procedure are provided in a separate body plethysmography manual provided to the designated study centers.

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 centers.

Serum will be collected pre-dose according to the schedule of study procedures (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 the 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 Blood 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 (including IL-5, Eosinophil-derived neurotoxin [EDN], and eotaxin)., Eosinophil-, basophil- and inflammation-related biomarkers of asthma may also be assessed.

Blood samples will be collected according to the schedule in Table 2 to evaluate the eosinophil progenitor cells by flow cytometry (subset of patients).

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

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

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

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

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

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

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

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

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

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

6. MANAGEMENT OF INVESTIGATIONAL PRODUCTS

6.1 Identity of investigational product(s)

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

Benralizumab and placebo administered in the study will be a clear to opalescent, colourless to yellow solution (Table 7).

Table 7 Identity of investigational product

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

6.2 Labelling

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

6.3 Storage

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

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

In the following cases:

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

The center staff should not use affected IP and should immediately contact an AstraZeneca representative for further guidance. Damaged IP should be documented via IWRS/IVRS (please refer to IWRS/IVRS manual for further details).

6.4 Accountability

The study drug provided for this study will be used only as directed in the CSP.

The study personnel will account for all study drugs dispensed to the patient.

The monitor will account for all study drugs received at the center, unused study drugs, and for appropriate destruction according to local procedures. Certificates of delivery, destruction, and/or return should be signed.

In case of malfunctioning accessorized pre-filled syringe (APFS), the site should contact the study monitor to initiate return of the APFS according to the procedure as described in the separate Shipment and Handling of Product Complaint Returns for IP.

6.5 Methods for assigning treatment groups

Randomization codes will be assigned strictly sequentially in each stratum (combination of eosinophil level and country/region) as patients become eligible for randomization.

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

6.6 Methods for ensuring blinding

The study will be conducted in double-blind, double-dummy fashion

All packaging and labelling will be done in such way as to ensure blinding. The following personnel will have access to the randomization list:

- the personnel carrying out the packaging and labelling of IMP
- the personnel generating the randomization list

The information in the randomization list will be kept from other personnel involved in the conduct of the study and in a secure location until the end of the study.

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 APFS.

Maintaining the blind to the patient's blood eosinophil counts

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

- Except for the Visit 1 screening eosinophil count (local laboratory), per protocol hematology will be run by the central laboratory with eosinophil and basophil counts redacted from the laboratory report (other than the Visit 1 laboratory report). Because complete knowledge of the remaining cell types could permit deduction of the 'eosinophil+basophil' compartment, monocyte counts will also be redacted from the report
- If the Investigator orders any local safety laboratory assessments, the requested tests should be restricted to the question at hand. For example, if a hemoglobin is desired, the Investigator should avoid ordering a complete blood cell count with differential
- **Handling of labs obtained during the treatment period but ordered outside of the clinical trial.** Center staff who are directly involved in the patient's management should remain blinded to any eosinophil, basophil, and monocyte results included as part of outside lab reports. To help ensure this, each investigational center will designate an individual (eg, administrator or another ancillary person) not directly involved in patient management, to receive and blind any eosinophil, basophil, and monocyte results prior to the report being handed over to the center staff involved in the patient's management and prior to filing as a source document. Similarly, eosinophil and basophil results must be redacted from all communications with the Sponsor.
- In cases where the Investigator requires an eosinophil, basophil, or monocyte count for managing safety issues he/she may order these tests. AstraZeneca should be notified of all such cases.

6.7 Methods for unblinding

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

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The

Investigator is to document and report the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

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

6.8 Investigational product administration and treatment compliance

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

The IP will be administered via SC injection at the study center 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 (refer to Section 3.6).

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

Before investigational product administration

Prior to each IP administration:

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

Investigational product administration

The IP will be administered at the study center on treatment visits and within visit windows as specified in the CSP. 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.

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

After investigational product administration

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

Conditions requiring investigational product administration rescheduling

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

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

6.9 Management of investigational product-related reactions

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

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

3. The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both, and at least 1 of the following: a) respiratory compromise or b) reduced BP or symptoms of end-organ dysfunction
4. Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced BP or associated symptoms, and/or persistent gastrointestinal symptoms
5. Reduced BP 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 may be drawn as soon as safely 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, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

7.1.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent 1 of the outcomes listed above

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

7.1.3 Recording of adverse events

7.1.3.1 Time period for collection of adverse events

All AEs, including SAEs, will be collected from the time the patient signs the informed consent throughout the treatment period and including the follow-up period (Visit 15, Week 36).

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 CSR. These activities should proceed as planned with ongoing AEs if necessary.

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

7.1.3.3 Variables

The following variables will be collected for each AE;

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 7.1.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not 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 the IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

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

7.1.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to the recording of a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

7.1.3.6 Adverse events based on examinations and tests

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

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

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

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

7.1.3.7 Symptoms of the disease under study

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

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

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

7.1.4 Reporting of serious adverse events

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

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

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

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

Once the Investigators or other center personnel indicate an AE is serious in the Web-based Data Capture (WBDC) system, an automated email alert will be sent to the designated AstraZeneca representative.

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

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

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

7.2 Overdose

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

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

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

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

7.3 Pregnancy

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

7.3.1 Maternal exposure

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

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

If any pregnancy occurs in the course of the study, then Investigators or other center personnel 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 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 and protocol violators identified.
- Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (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

For the primary endpoint of percentage reduction from baseline OCS dose, 70 patients per treatment arm are required to detect a difference between each of the benralizumab groups and the placebo group with 86% power using a two-sided 5% level Wilcoxon rank sum test. The sample size calculation is based on simulations using the OCS reduction data from Steroid Reduction with Mepolizumab Study (SIRIUS) (Bel et al 2014) which showed a median percentage reduction of 50% in the active treatment group compared with no reduction in the placebo group).

8.3 Definitions of analysis sets

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

8.3.1 All patients analysis set

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

8.3.2 Full analysis set

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

8.3.3 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 1 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 deviations (eg, disallowed medication) will be included in the PK analysis set. All PK summaries will be based on this analysis set.

8.3.5 Anti-drug antibodies analysis set

All patients in the safety analysis set who received at least 1 dose of benralizumab will be included in the ADA analysis set. Patients will be classified the same way as in the safety analysis set. All ADA summaries will be based on this analysis set. Both treatment induced and non-treatment induced (baseline) ADA responses will be summarized.

8.4 Variables for analyses

8.4.1 Calculation or derivation of efficacy variables

All efficacy objectives will be evaluated for the 28-week double-blind treatment period, defined as the period after administration of randomized IP at Visit 6 and the conclusion of Visit 14, inclusive.

8.4.2 Percentage reduction from baseline in oral corticosteroid dose

The primary variable is the percentage reduction from baseline in the final OCS dose while maintaining asthma control. The baseline OCS dose is defined as the dose upon which the patient is stabilized at randomization. The percentage reduction from baseline is defined as:

*{(Baseline dose–final dose)/baseline dose}*100%*

For patients who lost asthma control between Visits 13 and 14, the final dose will be set to 1 dose level higher than that which directly preceded the loss of asthma control.

Similarly, for patients who withdrew from the study, the final dose will be set to 1 dose level higher than that which directly preceded withdrawal.

8.4.3 Proportion of patients with ≥50% reduction from baseline in oral corticosteroid dose

For an individual patient, if the calculation above results in a value of 50% or greater, that patient will be classified as having at least a 50% reduction in daily OCS dose. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≥50% reduction at final visit/number of patients in treatment group

8.4.4 Proportion of patients with 100% reduction from baseline in oral corticosteroid dose

For an individual patient, if the calculation in Section 8.4.2 results in a value of 100%, that patient will be classified as having a 100% reduction in daily OCS dose. The proportion of such patients will be calculated for each treatment group as:

Number of patients with 100% reduction at final visit/number of patients in treatment group

8.4.5 Proportion of patients with ≤5 mg reduction from baseline in oral corticosteroid dose

For each treatment group, the number of patients with ≤5 mg reduction on daily oral corticosteroid use will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with ≤5 mg reduction at final visit / number of patients in treatment group

See Section 8.4.2 for the final OCS dose of patients who either lost asthma control between Visits 13 and 14 or withdrew from the study.

8.4.6 Proportion of patients with average final oral corticosteroid dose ≤5.0 mg daily

For each treatment group, the number of patients with average final OCS dose ≤5.0 mg daily will be calculated. The proportion of such patients will be calculated for each treatment group as:

Number of patients with average final OCS dose ≤5 mg daily at final visit / number of patients in treatment group

See Section 8.4.2 for the final OCS dose of patients who either lost asthma control between Visits 13 and 14 or withdrew from the study.

8.4.7 Forced expiratory volume in 1 second

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as secondary efficacy variables. The pre-BD measurements recorded at Visit 6 will be used as baseline FEV_1.

8.4.8 Rate of exacerbations

An asthma exacerbation is defined in Section 5.1.2. Refer to the SAP for exacerbation calculation rules.

The start of an exacerbation is defined as the start date of systemic corticosteroids or start date of an increased OCS dose that is used to treat an exacerbation, 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 an increased OCS dose that is used to treat an exacerbation 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 28-week double-blind treatment period will be used as response variable.

NB. If the patient is not fulfilling criteria for down titration listed in Section 5.1.1.1 and needs to be up titrated, the patient should up titrated by 1 level and this up titration should not be considered the start of an exacerbation.

An additional bolus/burst of systemic corticosteroid, emergency room visit 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 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 28 weeks; defined as the time from randomization to the date of Visit 14. For a patient lost to follow-up, this will be defined as the time from randomization to the time point after which an exacerbation could not be assessed.

For the production of summary statistics, the annual exacerbation rate per patient is calculated.

8.4.9 Proportion of patients with at least 1 exacerbation during the 28-week treatment period

The proportion of patients with ≥1 asthma exacerbation during the 28 weeks of treatment will also be analyzed. The proportion of such patients will be calculated for each treatment group as:

Number of patients with at least on exacerbation/number of patients in treatment group

8.4.10 Time to first exacerbation

Time from randomization to the first asthma exacerbation will also be analyzed, 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 t experience an asthma exacerbation during the treatment period will be censored at the date of their last visit during the 28-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients).

8.4.11 Time to first exacerbation requiring hospitalization

Time from randomization to the first asthma exacerbation requiring hospitalization will be analyzed, and is calculated as follows:

Start Date of first asthma exacerbation requiring hospitalization−Date of Randomization+1.

The time to first asthma exacerbation requiring hospitalization for patients who do not experience an asthma exacerbation requiring hospitalization during the treatment period will be censored at the date of their last visit during the 28-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients).

8.4.12 Time to first exacerbation requiring hospitalization or emergency department visit

Time from randomization to the first asthma exacerbation requiring hospitalization or ED visit will also be analyzed, and is calculated as follows:

Start Date of first asthma exacerbation requiring hospitalization or ED visit−Date of Randomization+1.

The time to first asthma exacerbation requiring hospitalization or ED visit for patients who do not experience an asthma exacerbation requiring hospitalization or ED visit during the treatment period will be censored at the date of their last visit during the 28-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients).

8.4.13 Number of days in hospital due to asthma

The total number of days in hospital due to asthma during the 28 weeks of treatment will be calculated for each patient.

8.4.14 Mean number days with oral corticosteroids taken for exacerbations

The total number of days with OCS taken for exacerbations during the 28 weeks of treatment will be calculated for each patient.

8.4.15 Blood eosinophil levels

The blood eosinophil level change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be calculated. The level recorded at Visit 6 will be used as baseline.

The eosinophil progenitor change from baseline to each of the post-randomization visits (post Visit 6) at which it is measured up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables (subset of patients). The level recorded at Visit 6 will be used as baseline.

8.4.16 Calculation or derivation of patient reported outcome variables

8.4.16.1 Asthma symptom score

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

8.4.16.2 Asthma Control Questionnaire

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

Patients will also be categorized according to the following limits (Juniper et al 2005):

- ACQ-6 (EOT – baseline) ≤-0.5 → Improvement
- -0.5 < ACQ-6 (EOT – baseline) <0.5 → No change
- ACQ-6 (EOT – baseline) ≥0.5 → 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 EOT in ACQ-6 ≤-0.5 and 0 otherwise. Furthermore, patients will be categorized according to their ACQ-6 EOT score as follows (Juniper et al 2006):

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

8.4.16.3 Asthma Quality of Life Questionnaire for patients 12 years or older

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 score from baseline (Visit 6) to each of the post-randomization periods.

Patients will also be categorized according to the following limits:

- AQLQ(S)+12 (EOT – baseline) ≥0.5 → Improvement
- -0.5 < AQLQ(S)+12 (EOT – baseline) <0.5 → No change
- AQLQ(S)+12 (EOT – baseline) ≤-0.5 → 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 EOT in AQLQ(S)+12 ≥0.5 and 0 otherwise.

8.4.16.4 Electronic diary variables

Asthma PROs (ACQ-6, AQLQ(S)+12), 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 mean of the last 14 days before randomization for the daily metrics. Each post-randomization period is defined as the period between 2 consecutive scheduled visits (until the Week 28 Visit 14). The change from baseline to each post-randomization period will be used as secondary efficacy variables.

8.4.17 Lung function as assessed through body plethysmography

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables. The level recorded at Visit 6 will be used as baseline. Variables include TLC, RV, VC, IC, and FRC.

8.4.18 Calculation or derivation of safety variables

8.4.18.1 Safety variables

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

Change from baseline (Visit 6) to each post-treatment time point where scheduled assessments are made will be calculated for relevant measurements. AEs will be summarized by means of descriptive statistics and qualitative summaries.

8.4.18.2 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 Adverse Events (OAEs) and reported as such in the CSR.

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

8.4.19 Calculation or derivation of 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. Due to the sparse sampling schedule and if data allows, population modeling will be performed to further characterize the PK of benralizumab. The potential influence of demographic covariates such as body weight, race, gender, and age will be explored. The impact of ADA on PK will also be assessed. The PK results will be provided in a clinical PK report (as an addendum to the CSR). The population modeling results will be presented in a separate pharmacometrics report.

8.4.20 Calculation or derivation of immunogenicity variables

ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer). Evaluations will be made at baseline (prior to benralizumab administration), and at routine time points during the treatment and follow up phases of the study or discontinuation. ADA titers by treatment group and visit will be summarized. **All ADA positive samples from the study will be tested for neutralizing antibodies (nAb) using a validated bioanalytical method.**

8.4.21 Exploratory variables

8.4.21.1 Sputum differential cell counts and biomarkers

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables. The level recorded at Visit 6 will be used as baseline. These variables include sputum cell differential counts, quantification of sputum cytokines and biomarkers, and assessment of eosinophil progenitor cells in sputum.

8.4.21.2 Serum biomarkers

The change from baseline to each of the post-randomization visits (post Visit 6) up to and including the end of 28-week double-blind treatment visit (Visit 14) will be used as exploratory variables. The level recorded at Visit 6 will be used as baseline.

8.5 Methods for statistical analyses

The analysis of the primary and secondary endpoints will include all data captured during the 28-week treatment period, including follow-up (where applicable), unless the patient withdraws consent to study participation, regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence. To emphasize the importance of collecting complete primary and secondary outcome data in all patients, the ICF form will ask that patients continue study assessments for the whole 28-week double-blind treatment period, including follow-up, even if they discontinue study treatment prematurely.

8.5.1 Testing strategy to account for multiplicity considerations

To account for multiplicity in testing the primary endpoint, the percentage reduction from baseline in OCS dose for the 2 dosing regimens, a testing strategy will be followed to control the overall type I error rate.

The testing strategy will be according to the Hochberg procedure (Hochberg 1988):

Step 1: Perform the hypothesis test of the percentage reduction in OCS for both doses against placebo. If the larger of the 2 p-values is less than 0.05, then reject both null hypotheses. If the larger of the 2 p-values is greater than 0.05, then proceed to Step 2.

Step 2: If the smaller of the 2 p-values is less than 0.025, then reject the null hypothesis associated with that p-value.

No adjustments will be made to p-values for any tests of secondary efficacy variables or safety variables. Any p-values reported for these variables will be considered nominal (ie, unadjusted).

8.5.2 Primary analysis method(s)

The primary efficacy variable is the percentage reduction from baseline in the patient's OCS dose, while maintaining asthma control. Each benralizumab dose regimen will be compared with placebo.

For each of the 2 benralizumab dose regimens, a Wilcoxon rank-sum test will be performed. The median difference in the percentage reduction of OCS dose between each benralizumab dose regimen and placebo, along with the 95% CI and p-value will be presented. In addition, the median percentage reduction in OCS dose and the corresponding 95% CI within each treatment group will be presented.

The above analyses will also be performed for patients with baseline blood eosinophils ≥300/μL while the multiplicity will not be adjusted for these analyses.

The percentage reduction in OCS dose will be summarized by treatment group in patients with baseline blood eosinophil counts ≥150-299/μL, 300-450/μL, and >450/μL separately.

8.5.3 Secondary analysis methods

8.5.3.1 Analysis methods for secondary efficacy variables

Secondary efficacy endpoints in this study are:

- The proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
- The proportion of patients with 100% reduction in average daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
- The proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control
- The proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control
- Proportion of patients with ≥1 asthma exacerbation
- Annual rate of asthma exacerbations
- Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization
- Time to the first asthma exacerbation
- Time to the first asthma exacerbation requiring hospitalization
- Time to the first asthma exacerbation requiring hospitalization or ED visit
- Number of days in hospital due to asthma
- Number of days with OCS taken for exacerbations
- Change from baseline in pre-bronchodilator FEV_1
- Change from baseline in morning and evening PEF
- Change from baseline in asthma symptom scores (total, daytime and nighttimes)

- Change from baseline in rescue medication use
- Change from baseline in the number of nights with awakening due to asthma requiring rescue medication
- Change from baseline in ACQ-6
- Proportion of ACQ-6 defined responders at Week 28
- Change from baseline in AQLQ(S)+12
- Proportion of AQLQ(s)+12 defined responders at Week 28
- TLC, RV, VC, IC, FRC

The secondary efficacy endpoints will be summarized by treatment group in patients with baseline blood eosinophil counts ≥150-299/μL, 300-450/μL, and >450/μL.

For the following variables, 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/region: the proportion of patients with ≥1 asthma exacerbation during the 28 weeks of treatment; the proportion of patients with ≥50% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with 100% reduction in daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6, while maintaining asthma control; the proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14, while maintaining asthma control.

Annual rate of asthma exacerbations will be analysed using a negative binomial model. The number of asthma exacerbations experienced by a patient during the 28-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. The model will include covariates of treatment group, country/region, and number of exacerbations in the year before the study. 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. This analysis will only be performed if there is a sufficient number of patients who have multiple exacerbations.

Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization will be analysed similarly as for annual rate of asthma exacerbations.

Time to first asthma exacerbation will be analysed 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/region, and number of exacerbations in the year before the study.

Time to first asthma exacerbation requiring hospitalization and time to first asthma exacerbation requiring hospitalization or ED visit will be analysed similarly as for time to first asthma exacerbation.

Change from baseline in pre-bronchodilator FEV_1 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-BDFEV_1 and at least 1 post-randomization pre-BD FEV_1. 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/region and baseline pre-BD FEV_1 will be used 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 pre-BD FEV_1+country/region+visit +treatment*visit.

The following variables will be analysed separately using a similar model as the above model for change from baseline in pre-BD FEV_1: Change from baseline in asthma symptom total score, daytime score and night time score, total rescue medication use, change from baseline in the number of nights with awakening due to asthma requiring rescue medication, change from baseline in morning and evening PEF, and change from baseline in ACQ-6 and AQLQ(s)+12.

Responder variables for ACQ-6 (yes/no) and AQLQ(S)+12 (yes/no) will be analysed using a logistic regression model with factors of treatment, country/region, and the baseline value as a covariate.

8.5.4 Analysis method for blood eosinophil levels

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

8.5.5 Analysis methods for exploratory variables

Exploratory endpoints in this study will be obtained from sputum collection and body plethysmography and include (subset of patients):

- sputum cell differential counts
- quantification of sputum cytokines and biomarkers
- assessment of eosinophil progenitor cells in sputum

Other exploratory endpoints will be obtained from blood and include:

- assessment of eosinophil progenitor cells (subset of patients)
- serum biomarkers

Raw values and change from baseline for the above indicated sputum, blood endpoints, and lung volume measurements will be summarized by treatment group and study visit. Measurements may also be plotted over time.

8.5.6 Analysis methods for safety variables

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

Laboratory safety variables will be summarized using standard summary statistics and plots as appropriate.

Other safety variables will be summarized as appropriate. Further details will be provided in the SAP.

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

8.5.7 Subgroup analysis (if applicable)

Full details of subgroup analyses will be pre-specified in the SAP.

8.5.8 Interim analysis and Data Monitoring Committee (if applicable)

No interim analyses are planned.

8.5.9 Sensitivity analysis

Full details of the sensitivity analysis will be pre-specified in SAP.

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

8.7 Data safety monitoring board

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

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study center personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP 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 utilized.

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

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

9.2 Monitoring of the study

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual, and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the center needs information and advice about the study conduct.

9.2.1 Source data

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

9.2.2 Recording of data

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

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

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

9.2.3 Study agreements

The Principal Investigator at each/the study center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

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

9.2.4 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

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

The study is expected to start in Q2 2014 and to end by Q3 2016.

The study may be terminated at individual study centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca

may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with benralizumab.

Database lock and unblinding for the CSR will occur after the last subject has completed the EOT or IPD visit. If, at this time, there are any patients who do not elect to continue in the separate extension study (D3250C00021), and have yet to complete final study-related assessments at the safety follow-up (Visit 15), these assessments are still to be conducted and the data will be listed separately in an addendum to the CSR.

9.4 Data management by AstraZeneca

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

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

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

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

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Patient data protection

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

10.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final CSP, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The

Investigator will ensure the distribution of these documents to the applicable EC and to the study center staff.

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

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

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

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

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

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

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

Each Principal Investigator is responsible for providing the ECs/Institutional Review Board (IRB) with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each study center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(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 ICF 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 ICF that is approved by an EC.

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 CSP, then these changes will be documented in a CSP amendment and, where required, in a new version of the CSP (Revised CSP).

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

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

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

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

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the study center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, ICH guidelines, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency or other body about an inspection or an audit at the study center.

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Clinical Study Protocol Appendix B

Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00020
Edition Number	1.0
Date	10 January 2014

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

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Clinical Study Protocol Appendix C

Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00020
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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

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

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

TABLE OF CONTENTS PAGE

1. INTRODUCTION

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

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

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

2. DEFINITIONS

Potential Hy's Law (PHL)

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

Hy's Law (HL)

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

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

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

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

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

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

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

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

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Notify the AstraZeneca representative who will inform the central Study Team

Follow the subsequent process described is Section 4.2 of this Appendix

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

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

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

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

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

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

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

If Yes:

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

- If there is no significant change no action is required

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

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

8. REFERENCES

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

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

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Clinical Study Protocol Appendix E	
Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00020
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Date	10 April 2015

Appendix E
Background Therapy Equivalence Table

Estimated daily dosage for inhaled corticosteroids *

Asthma Therapy	**Total Daily Dose (µg/day)**	
Inhaled Corticosteroid	Medium	**High**
Beclomethasone dipropionate	>500 - 1000	**>1000 -** 2000
Beclomethasone HFA	>240 - 480	**>480**
Beclomethasone dipropionate (Fostair)	>200 - 400	**>400** - 800
Ciclesonide	>160 - 320	**>320** - 1280
Triamcinolone acetonide	>1000 - 2000	**>2000**
Flunisolide	>1000 - 2000	**>2000**
Fluticasone propionate	>250 - 500	**>500** - 1000
Fluticasone propionate HFA	>364 - 440	**>440**
Budesonide	>400 to 800	**>800** - 1600
Budesonide, if as delivered dose (eg Symbicort)	>320 to 640	**>640** - 1280
Mometasone furoate	≥400	**≥800**

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Clinical Study Protocol Appendix F	
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Appendix F
Anaphylaxis: signs and symptoms, management

1. INTRODUCTION

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

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

2. CLINICAL CRITERIA FOR DEFINING ANAPHYLAXIS AND IMMUNE COMPLEX DISEASE

Anaphylaxis

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

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

   AND AT LEAST ONE OF THE FOLLOWING

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

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

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

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

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

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

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

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

Immune Complex Disease

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

3. SIGNS AND SYMPTOMS AND MANAGEMENT OF ACUTE ANAPHYLAXIS

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

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

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles
- Rhinorrhea
- Change in voice

- Metallic taste
- Nausea, vomiting, diarrhea, abdominal cramps and bloating
- Lightheadedness
- Headache
- Uterine cramps
- Generalized warmth

4. MANAGEMENT OF ACUTE ANAPHYLAXIS

4.1 Immediate intervention

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

4.2 Possibly appropriate, subsequent measures depending on response to epinephrine

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

(b) Establish and maintain airway.

(c) Administer oxygen.

(d) Establish venous access.

(e) Normal saline IV for fluid replacement.

4.3 Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion.

(b) Consider H1 and H2 antihistamines.

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

(d) Consider systemic corticosteroids.

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

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

(g) Consider atropine for symptomatic bradycardia.

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

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

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

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Clinical Study Protocol Appendix G	
Drug Substance	Benralizumab (MEDI-563)
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Appendix G
Restricted and prohibited medications

PROHIBITED AND RESTRICTED MEDICATIONS

Asthma medication restrictions

Table 1 Asthma medication restrictions

Medication	Prohibited/restricted	Details
Maintenance of asthma controller medications (ICS-LABA)	Restricted	Changes in dose and regimen should not be done from enrolment and throughout the study treatment (unless there is a medical need as judged by the Investigator) Usual ICS-LABA should not be taken prior to scheduled spirometry, ECG and home peak flow assessments (to be administered once assessments are completed)
Short acting beta-agonists (SABA)	Restricted	Rescue use of SABA administered via nebulisation is discouraged, except as urgent treatment during an asthma exacerbation. SABA should not be used within 6 hours prior to scheduled spirometry, ECG and home lung function assessments.
Additional Maintenance Controllers (eg LTRAs, tiotropium, cromone, theophylline)	Allowed with restriction	Stable dose for 2 weeks prior to randomisation and stable dose during the treatment period (except during the treatment of exacerbations)
Short acting anticholinergics (e.g. ipratropium)	Restricted	Not allowed from enrollment and throughout the study as a rescue treatment for worsening asthma symptoms outside of managing an asthma exacerbation event May be used for managing an asthma exacerbation event.
Long-acting beta-agonists as a reliever (e.g. Symbicort	Prohibited	Not allowed from enrolment and

Maintenance and Reliever Treatment)		throughout the study duration
Zileuton	Prohibited	Not allowed within 30 days of Visit 1 and during treatment period.

Other medication restrictions

Table 2 Other medication restrictions

Medication	Prohibited/restricted	Details
Live Attenuated Vaccines	Prohibited	Not allowed within 30 days of Visit 1;during treatment period and within 4 months (5 half-lives) after the last dose of the investigational product
Inactive/killed vaccinations (e.g. inactive influenza)	Restricted	Not allowed within the 7 days before or within the 7 days after any study visit
Any immunomodulators or immunosuppressives	Prohibited	Not allowed 3 Months or 5 Half Lives (whichever is longer) prior to Visit 1; during treatment period; 3 Months or 5 Half Lives (whichever is longer) after Last Dose
Blood products or immunoglobulin therapy	Prohibited	Not allowed 30 days prior to date of ICF;during treatment period
Any marketed (eg omalizumab) or investigational biologic treatment	Prohibited	Not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1; during treatment period; 4 months or 5 half-lives (whichever is longer) after the last dose of the investigational product
Other investigational Products (including investigational use of an approved drug)	Prohibited	Not allowed 30 Days or 5 Half Lives (whichever is longer) prior to Visit 1; during treatment period
Allergen Immunotherapy	Restricted	Allowed if on stable therapy for at least 30 days prior to date of ICF; no anticipated changed during treatment

Medication	Prohibited/restricted	Details
		period
Roflumilast	Prohibited	Not allowed 30 days prior to Visit 1 and during treatment period
Oral or ophthalmic non-selective β-adrenergic antagonist (e.g. propranolol)	Prohibited	Patients currently using any oral or ophthalmic β-adrenergic antagonist at the time of enrolment are not eligible for the study. Not allowed during treatment period.

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Clinical Study Protocol Appendix H	
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Appendix H
OCS Dose Therapy Equivalence Table

Estimated OCS Dose Therapy Equivalence

Asthma Therapy OCS	Approximate equivalent Dose
Oral Prednisone	10 mg
Cortisone	50 mg
Hydrocortisone	40 mg
Methylprednisolone	8 mg
Prednisolone	10 mg
Triamcinolone	8 mg
Betamethasone	1.2 mg
Dexamethasone	1.5 mg
Budesonide	2.25 mg
Deflazacort	12 mg