Clinical Study Protocol	
Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00036
Version	5.0
Date	18 Dec 2020

A Multicentre, Randomised, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) Added to Medium to High-dose Inhaled Corticosteroid Plus Long-acting β_2 Agonist in Patients with Uncontrolled Asthma

Sponsor: PPD

VERSION HISTORY

DOCUMENT HISTORY	
Document	**Date**
Version 5.0	18-Dec-2020
Version 4.0	17-Dec-2019
Version 3.0	25-Apr-2018
Version 2.0	28-Nov-2016
Original Protocol (Version 1.0)	25-Nov-2014

The Protocol Amendment Summary of Changes Table before Version 5.0 is located in Appendix H.

Version 5.0 (18-Dec-2020)

This amendment is considered to be substantial based on the criteria set fort in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of European Union

Overall Rationale for the Amendment:

The primary rationale for this amendment is to add study mitigation language which will provide sites with measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to the study integrity.

Version 5.0, 18 December 2020		
Section # and name	Description of Change	Brief rationale for Change
Protocol Synopsis	Extend the estimated date of last patient completed to Q1 2023	Extend the study timeline based on the current recruitment plan
Protocol Synopsis/Section 1.4 Study Design/Section 3.3 patient enrolment and randomisation	Change the percentage of China patients from approximately 80% to at least 70%	Allow patient redistribution and competitive recruitment among countries, while keeping

	Remove specific regions	the overall sample size the same.
Protocol Synopsis Strata closure process/Section 1.4 Study Design	Include "other asthma controllers" in patient maintenance therapy	Clarify that asthma controllers should be stable throughout the study
Protocol Synopsis Objectives/Section 2.2 Secondary Objectives	Including incidence of nAb, ADA titer into the secondary objective of characterizing immunogenicity of benralizumab	Clarify the outcome measures for immunogenicity
Section 1.3 Benefit/risk and ethical assessment	Add statement of no apparent impact of ADA on overall benralizumab safety or efficacy in the previous Phase 3 studies. Add information about important risk of serious hypersensitivity reactions.	Keep consistent with updated IB
Section 3.1 Inclusion Criteria 3	Update the time period of female patients using an effective form of birth control from 16 weeks to 12 weeks. Update contraceptive methods wording to removing brand name, etc.	Keep consistent with current knowledge of benralizumab PK parameters Follow CTFG recommendation for contraception wording revision.
Section 3.1 Inclusion Criteria 4	Delete the criteria of male contraception requirement.	Keep consistent with current knowledge of benralizumab
Section 3.1 Inclusion Criteria 8 (inclusion criteria 9 in CSP V4)	Change documented post-bronchodilator (post-BD) reversibility in FEV1 of >12% and >200 ml to ≥ 12% and ≥200 ml	Keep consistent with other sections of the protocol or other sections

Section 3.2 Exclusion Criteria 10	Remove ALT and AST requirement	Only keep one exclusion criteria to liver function avoiding duplication
Section 3.2 Exclusion Criteria 12	Change the criteria for current smokers or former smokers	Specify the criteria for former smokers
Section 3.2 Exclusion Criteria 27	Update ALT and AST requirement	Keep it consistent with requirement of liver disease
Section 3.6 Methods for ensuring blinding	Add statement to specify unblinded treatment data will be available to bioanalytical lab personnel for PK sample analysis during the conduct of study.	Facilitate the new process that PK sample will be analysed only for patients receiving benralizumab and to clarify how these data will remain blinded to the study team and site during the study conduct.
Section 3.8.2 Other medication restrictions	Update the time period of vaccine receipt from 16 weeks to 12 weeks	Keep consistent with current knowledge of benralizumab PK parameters
Section 3.8.3 Other restrictions	Update the time period of using effective contraceptive methods from 16 weeks to 12 weeks Delete male contraception restriction.	Keep consistent with current knowledge of benralizumab PK parameters
Section 3.9 Discontinuation of investigational product/Section 7.4 IP administration and treatment compliance	Remove the criteria of 2 consecutive doses IP missed for discontinuation Add the statement of how to deal with the cases of a patient missing more than 2 doses within a calendar year	Make consistent with contents in recent benralizumab protocols

Section 3.9.1 Procedures for discontinuation of a patient from investigational product	Re-organize the wording to make it easy to be understood.	For clarity.
Section 3.9.1 Procedures for discontinuation of a patient from investigational product/Section 4.2 Treatment period	Update the time frame of IPD visit within 8 weeks +7 days after the last dose of IP for all patients	Keep the same time frame for all scenarios of IP discontinuation
Section 4.1.1 Enrolment (Visit 1)	Add the statement of EOS retest	Re-screen because of eosinophil is replaced by eosinophil retest to reduce the burden of subjects
Section 4.1.3 Re-screening	Remove the statement of rescreening patients with EOS < 300 cell/uL at Visit 1	Rescreening is not needed since EOS retest is added
Section 4.4 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	New wording was added which would give guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity.	The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. This section details the measures that may be implemented if a patient is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the patient, maintaining compliance with GCP, and minimizing risks to study integrity, These changes will only be initiated at a time of study disruption.

Section 5.1.2 Spirometry	Change "2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded" to "the best effort that meets the ATS/ERS acceptability and reproducibility criteria will be analysed".	Keep consistent with company standard process
Section 5.3.2.2 Asthma control questionnaire (ACQ-6)	Change ACQ-6 score range from "between 0.75 and <=1.5" to between 0.75 and <1.5". Change the score which indicates not well controlled asthma to >= 1.5 Remove ACQ-6 between Visit 2 and Visit 3 on a weekly basis	Keep consistent with guideline Update due to no plan to analyse ACQ-6 between Visit 2 and Visit 3
Section 5.3.5 Pharmacokinetics	Add statement to specify PK sample will be analysed only for patients receiving benralizumab.	Specify the new process for PK lab sample analysis.
Section 5.3.8 Patient Testing Due to Public Health Crisis	Section included if patient testing is performed due to the public health crisis, the results may be documented for this study.	Section added for test results secondary to public health crisis to be collected allowing for an evaluation of the public health crisis on the study.
Section 6.2 Definitions of serious adverse event	Additional malignancy relevant text added to be consistent with latest CSP template	Follow updated latest CSP template
Section 6.5 Overdose	Update the definition of overdose	Follow latest IB content.

Section 6.6.2 Paternal Exposure	Remove male contraception requirement wording	Keep consistent with current knowledge of benralizumab
Section 6.8 Device Constituent Deficiencies	Add the section of Device Constituent Deficiencies	Benralizumab is considered a drug-device combination (biologic device combination) for regulatory reporting guidelines. Due to new regulations in EU and US, updates to respective CSP section was done.
Section 7.4 IP administration and treatment Compliance	Remove the criteria of 2 consecutive doses IP missed for discontinuation Add the statement of how to deal with the cases of a patient missing more than 2 doses within a calendar year	Make consistent with contents in recent benralizumab protocols
Section 7.4 IP administration and treatment Compliance/Section 7.7 Management of investigational product-related reactions	Remove the time limitation of observing acute drug reaction	Keep consistent with current knowledge of benralizumab
Section 8.5 Methods for statistical analyses	Add “additional analyses assessing the impact of Cases of Civil Crisis , Natural Disaster, or Public Health Crisis (e.g. SARS-CoV-2) may be included in the SAP”.	Specify analyses will be added to assess the COVID-19 impact and details will be present in SAP.
Section 8.5.2.1 Analysis methods for secondary efficacy variables	Replace "The ACQ-6 will be analyzed in terms of change from baseline to end of treatment, change from baseline to overall	Clarify that change from baseline is compared with each post-baseline visit not compared with overall post-baseline mean and to

	post-baseline mean, and responder status at EOT (i.e. baseline to EOT ACQ-6 score change of >=-0.5 points), and asthma symptom control status at EOT." by "The ACQ-6 will be analyzed in terms of change from baseline to end of treatment, change from baseline to each of post-randomisation periods, responder status at EOT (i.e. change from baseline to EOT<=-0.5), and asthma symptom control status at EOT (see Section 8.4.3.2 for categorization)."	correct the responder definition to be consistent with Section 8.4.3.2.
Section 8.5.3 Subgroup analysis	Add subgroup factor 'Nasal polyps' and remove subgroup factor 'Race'.	The subgroup factor 'Nasal polyps' is meaningful and explored in other Benralizumab studies. "Race" is not meaningful as all the countries participating are in Asia.
Appendix D Anaphylaxis: definition, signs, symptoms and management Introduction	Change the wording of Appropriate drugs in site. Update monitoring time frame.	Keep consistent with current knowledge
Appendix G Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	New wording is added, which would give guidance on how the study could continue in the event of a serious disruption with details of mitigation that	The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. This section details the measures

	could be employed to ensure study continuity.	that may be implemented if a patient is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the patient, maintaining compliance with GCP, and minimizing risks to study integrity, These changes will only be initiated at a time of study disruption.
Appendix H Protocol Amendment History	New Appendix is added to put the protocol amendment history from V1 to V4	Follow the latest CSP template

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

A Multicentre, Randomised, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) Added to Medium to High-dose Inhaled Corticosteroid Plus Long-acting β_2 Agonist in Patients with Uncontrolled Asthma

International Co-ordinating Investigator

PPD

Study site(s) and number of patients planned

This study will be conducted regionally in approximately 90 study centres in China and other countries. Target is to randomise approximately 666 patients, among which at least 70% patients will be randomised from China.

Study period		Phase of development
Estimated date of first patient enrolled	Q2 2017	III
Estimated date of last patient completed	Q1 2023	III

Study design

This is a randomised, double-blind, parallel group, placebo-controlled study designed to evaluate the efficacy and safety of a fixed 30 mg dose of benralizumab administered subcutaneously (SC) for patients with a history of asthma exacerbations and uncontrolled asthma receiving medium to high-dose inhaled corticosteroid plus long-acting β2-agonist (ICS-LABA) with or without oral corticosteroids and additional asthma controllers. Approximately 666 patients will be randomised, among which at least 70% patients will be recruited from China. Patients will be stratified by country/region , age group (adult or adolescent), and peripheral blood eosinophil count at time of Visit 1 (<300 or ≥300 cells/μL).

Strata closure process:

1 The eosinophil <300/μL stratum will be closed to all the patients from China when the total number of Chinese patients in the stratum reaches approximately 166.

2 The eosinophil <300/μL stratum will be closed to the patients from all countries when the total number of patients in the eosinophil <300/μL stratum reaches approximately 222.

3 The whole study will be closed for recruitment when the total number of patients in the eosinophil ≥300/μL stratum reaches approximately 444, with at least 70% Chinese patients in the stratum.

After initial enrolment and confirmation of entry criteria, patients will proceed to the run-in period of a minimum 4 weeks to allow adequate time for all the eligibility criteria to be evaluated. Patients, who meet eligibility criteria, will be randomised to a 48-week treatment period. Patients will be maintained on their currently prescribed medium to high-dose ICS-LABA therapy and other asthma controllers, without change, from visit 1 until the end of the study.

A follow-up visit will be conducted at Week 56.

Objectives

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

a For the purpose of the protocol, worsening of asthma is defined as new or increased symptoms and/or signs (examination or lung function) that can be either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (diary-driven). The Electronic patient reported outcome (ePRO) device will be programmed to alert both the patient and study centre when certain pre-specified worsening thresholds are crossed including: decrease in morning peak flow ≥30% on at least 2 of 3 successive days compared with baseline (last 10 days of run-in), and/or a ≥50% increase in rescue medication or 1 new or additional nebulized β_2 agonist on at least 2 of 3 successive days compared with the average use for the previous week and/or nocturnal awakening due to asthma requiring rescue medication use for at least 2 of 3 successive nights, and/or; an increase in total asthma symptom score (the sum of day time [evening assessment] and night time [morning assessment] of at least 2 units above the run-in average (last 10 days of run-in), or the highest possible score (daily score of 6), on at least 2 of 3 successive days).

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

Secondary Objective:	**Outcome Measure:**
To assess the effect of benralizumab on pulmonary function	Pre-bronchodilator Forced expiratory volume in 1 second (FEV_1) [b]
To assess the effect of benralizumab on asthma symptoms and other asthma control metrics (as per the ePRO)	• Asthma symptom score (total[b], day time, and night time) • Rescue medication use • Home lung function (morning and evening PEF) • Nights with awakening due to asthma • Asthma Control Questionnaire 6 (ACQ-6)
To assess the effect of benralizumab on other parameters associated with asthma exacerbations	Time to first asthma exacerbation and proportion of patients with ≥1 asthma exacerbation
To assess the effect of benralizumab on health-related quality of life	St. George's Respiratory Questionnaire (SGRQ)
To assess the effect of benralizumab on emergency room/urgent care visits and hospitalizations due to asthma	Annual rate of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalization
To evaluate the effect of benralizumab on health care resource utilization	Asthma specific resource utilization (eg, unscheduled physician visits, use of other asthma medications)
To characterize the PK and immunogenicity of benralizumab	• PK: Serum trough concentrations • Immunogenicity: Incidence of anti-drug antibodies (ADA) and neutralizing antibodies (nAb), ADA titer.
To assess the impact of benralizumab on blood eosinophil levels	• Blood eosinophils

b Key secondary efficacy endpoints

Safety Objective:	**Outcome Measure:**
To assess the safety and tolerability of benralizumab	• Adverse event (AE)/ Serious Adverse Event (SAE) • Laboratory variables • Electrocardiogram (ECG) • Vital Signs

Target patient population

Male and female patients 12-75 years of age with asthma inadequately controlled by treatment with medium to high-dose inhaled corticosteroid plus long-acting β2-agonist with or without oral corticosteroids and other asthma controller medications.

Duration of treatment

Following initial enrolment, the patient will enter a minimum 4-week run-in period, which is followed by a 48-week double-blind, randomised treatment period, with the last dose of benralizumab/placebo administrated at Week 40. At Week 48, an End of Treatment (EOT) visit will be conducted. A Follow-up visit will be conducted at Week 56.

The total planned study duration is approximately 63 weeks.

Investigational product, dosage and mode of administration

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

Comparator, dosage and mode of administration

For all patients, benralizumab or matching placebo solution for injection in an APFS will be administered at the study site SC every 4 weeks for the first 3 doses and then every 8 weeks thereafter.

Statistical methods

The primary efficacy variable is the annual asthma exacerbation rate. Exacerbation rate in the benralizumab group will be compared to exacerbation rate in the placebo group using a negative binomial model including covariates of treatment group, region (China/non-China), number of exacerbations in the year before the study, and the use of maintenance oral corticosteroids (yes/no). The logarithm of the follow-up time will be used as an offset variable in the model. Change from baseline in pre-bronchodilator FEV_1 at Week 48 will be compared between benralizumab and placebo group using a repeated measures analysis. Treatment group will be fitted as the explanatory variable, and region (China/non-China), baseline pre-bronchodilator FEV_1, visit, visit□by-treatment interaction, and the use of maintenance oral

corticosteroids (yes/no) will be fitted as covariates. Visit will be fitted as a categorical variable. Change from baseline in asthma symptom total score at Week 48 will be analysed using a similar model as the model for change from baseline in pre-bronchodilator FEV_1. The primary endpoint and the 2 key secondary endpoints (change from baseline in pre-bronchodilator FEV_1 and asthma symptom total score at Week 48) will be analysed primarily using the patients with baseline blood eosinophil counts ≥300/μL in the full analysis set according to a gate-keeping procedure. Full analysis set includes all randomised patients who received at least one dose of investigational product (IP). In addition, the exacerbation rate and the 2 key secondary endpoints will also be summarized in patients with baseline blood eosinophil counts < 300/μL, < 150/μL, 150-299/μL, 300-449/μL and ≥450/μL separately.

The study will randomise patients with baseline blood eosinophil counts ≥300/ μL and <300/ μL at a ratio of about 2:1 and the study is powered for the primary efficacy analysis of the patients with baseline blood eosinophils ≥300/ μL. For the primary endpoint, annual asthma exacerbation rate, approximately 222 adult and adolescent patients with baseline blood eosinophil counts ≥300/μL per treatment arm (approximately 444 in total) will need to be randomised to achieve 90% power of CCI [redacted] According to the 2:1 ratio, the study will also randomise approximately 111 patients/arm (approximately 222 in total) with baseline blood eosinophil counts <300/μL. Approximately 666 patients are expected to be randomised in the study with at least 70% of patients to be enrolled from China.

The efficacy and safety analyses will comprise both adult and adolescent patients. All safety parameters will be analysed. Safety analyses will be based on the safety analysis set, defined as all patients who received at least 1 dose of IP.

There is no interim analysis planned for this study. The study will remain blinded until database lock.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
Beta-hCG	Beta- human chorionic gonadotropin
BP	Blood pressure
BT	Bronchial thermoplasty
BUN	Blood urea nitrogen
CFC	Chlorofluorocarbon
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CRO	Contract research organization
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTFG	Clinical Trials Facilitation and Coordination Group
DPI	Dry Powder Inhaler
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EC90	Benralizumab serum concentration corresponding to 90% of maximum efficacy
ED	Emergency department
ED90	Benralizumab dose corresponding to 90% of maximum efficacy
EOS	Eosinophil
EOT	End of Treatment
ePRO	Electronic patient reported outcome
EXACA	Exacerbation eCRF
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
Gamma-GT	Gamma-glutamyl transpeptidase
GCP	Good Clinical Practice

Abbreviation or special term	Explanation
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
GLI	The Global Lung Function Initiative
HCP	Health care provider
HFA	Hydrofluoroalkane
HRU	Healthcare Resource Utilization
HRQoL	Health-related quality of life
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IL	Interleukin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-5Rα	Interleukin-5 receptor alpha subunit
IM	Intramuscular
IMP	Investigational Medicinal Product
ICI	International Coordinating Investigator
IP	Investigational Product
IPD	Premature IP Discontinuation
IRB	Institutional Review Board
ISF	Investigator Study File
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-acting β_2 agonists
LAMA	Long-acting anti-muscarinic
LDH	Lactate dehydrogenase
LDL cholesterol	Low density lipoprotein cholesterol
LTRA	Leukotriene receptor antagonists
MED	Medication
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
nAb	Neutralizing antibodies
NYHA	New York Heart Association
OCS	Oral corticosteroids
pECG	Paper print-out ECG
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
PN	Predicted normal
Post-BD	Post-bronchodilator
Pre-BD	Pre-bronchodilator
PRO	Patient reported outcome
RBC	Red blood cell
SABA	Short-acting β_2 agonists
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGRQ	St. George's Respiratory Questionnaire
TEAEs	Treatment Emergent Adverse Event
TLC	Total lung capacity
ULN	Upper limit of normal
UNS	Unscheduled
WBC	White blood cell
WBDC	Web-based Data Capture
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

1.1.1 Background

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

The current approach to anti-inflammatory controller therapy in asthma is based on a step-wise intensification of a daily maintenance regimen primarily centred around inhaled

corticosteroids (ICS) and leukotriene receptor antagonists (LTRA), with the addition of long-acting β_2 agonists (LABA) in patients with more severe asthma (Global Initiative for Asthma (GINA 2014, NAEPP 2007). Despite treatment per management guidelines, up to 50% of patients have asthma that is not well-controlled (Bateman et al 2010). This results in considerable impact on quality of life, disproportionate use of healthcare resources, and adverse reactions from regular systemic steroid use. Symptom control in children and adolescents with asthma can be similarly challenging, due in part to the limitations of current therapeutic modalities. Longer treatment courses, over a period of months or years, and higher medication doses may be required to achieve the maximum possible improvement in lung function in children older than 5 years (GINA 2014). 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 (Bateman et al 2010, 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, Pavord et al 2012). These promising results support continued development of therapies targeting the IL-5 pathway in eosinophilic asthmatics unresponsive to standard therapies.

In contrast to anti-IL-5 therapies, benralizumab (MEDI-563) is a humanized, afucosylated, monoclonal antibody that binds specifically to the human IL-5 receptor alpha subunit (IL-5Rα) on the target cell. The IL-5 receptor (IL-5R) is expressed almost exclusively on the surface of eosinophils and basophils (Takatsu et al 1994, Toba et al 1999). Afucosylation confers enhanced antibody-dependent cellular cytotoxicity (ADCC) which results in highly efficient eosinophil depletion by apoptosis (Kolbeck et al 2012). Single and repeated doses of benralizumab in mild to severe asthma patients during early development or Phase 1/2 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 (IB).

1.1.2 Rationale for conducting this study

The treatment options for patients who remain uncontrolled by ICS-LABA are extremely limited. In previous clinical studies, benralizumab administration resulted in rapid and prolonged depletion of eosinophils in the peripheral blood and in the asthmatic airway with associated improvements in multiple metrics of asthma control. The magnitude of clinical improvement was positively correlated with baseline blood eosinophil counts and was most consistently observed in patients with absolute blood eosinophil counts ≥300/μL. In the pivotal studies (Bleecker et al 2016, FitzGerald et al), compared with placebo, benralizumab 30 mg administered subcutaneously (benralizumab 30 mg every 4 weeks for the first 3 doses and then every 8 weeks thereafter) significantly reduced the annual asthma exacerbation rate, improved asthma symptom and lung function (pre-bronchodilator FEV_1). The purpose of this trial is to confirm the efficacy and safety of benralizumab administration in asthma patients who are otherwise uncontrolled on current standard of care therapy. The question of the baseline blood eosinophil level that predictably ensures the clinical benefit in patients will also be addressed in the study by inclusion of patients with blood eosinophil counts ≥300/μL and <300/μL.

1.2 Rationale for study design, doses and control groups

This is a regional study designed to investigate the safety and efficacy of the fixed dose benralizumab (30 mg) administered subcutaneously (SC) every 4 weeks for the first 3 doses and then every 8 weeks thereafter in exacerbation-prone asthma patients who remain uncontrolled on medium to high-doses ICS-LABA with or without oral corticosteroids and other asthma controller(s).

Primary efficacy will be determined based on reduction in the rate of asthma exacerbations over 48 weeks for benralizumab versus placebo. In order to avoid biasing the results, the study will be randomised and double-blinded with stratification by age group (adult or adolescent), country/region and eosinophil category (≥300/μL/<300/μL).

The study will randomise patients with screening blood eosinophils ≥300/μL and <300/μL at a ratio of about 2:1. The 2:1 stratification of patients with eosinophil counts ≥300/μL and <300/μL is intended as a means of enriching the population for patients most likely to respond to benralizumab (ie, ≥300/μL), while still accommodating patients below this threshold in order to help understand where additional benefit drops off.

The benralizumab dose (30 mg SC, fixed) and the maintenance regimens are based on all available safety, efficacy and immunogenicity data, as well as population exposure-response modeling, and stochastic trial simulations from earlier phase benralizumab trials. In particular, Phase 2b MI-CP220 study (Castro et al 2014) showed that fixed doses of

benralizumab ≥20 mg administered every 8 weeks were clinically effective. The potential impact on efficacy of anti-drug antibodies and body weight on pharmacokinetics (PK) were incorporated in a population PK model. Analyses of efficacy endpoints (asthma exacerbations, forced expiratory volume in 1 second [FEV_1] and ACQ) suggest 30 mg every 8 weeks (with the first 3 doses administered every 4 weeks) is an effective and tolerable dose for further testing in patients with severe asthma. This dose corresponds to the ED_{90} (benralizumab dose corresponding to 90% of maximum efficacy) for asthma exacerbation reduction and ACQ, and maintains a steady-state PK exposure close to EC_{90} (benralizumab serum concentration corresponding to 90% of maximum efficacy) levels for FEV_1 and ACQ. Asthma manifestations and responses to existing treatments in adolescents and adults are similar. With a 40 kg lower body weight limit, the projected PK exposure in adolescents mostly overlaps with that in adults. The PK difference between adolescents and adults is expected to be small and within the normal range of between-patient variability among adults. Further, the 100 mg Q8W top dose investigated in Phase 2b study provided adequate exposure coverage. To date, there are no data suggesting a dose- or exposure-related increase in treatment-emergent adverse events (TEAEs) with benralizumab in adult patients. As such, adolescent patients (≥40kg) will receive the 30 mg adult dose in Phase 3 studies.

Other stable asthma therapies on top of ICS-LABA that are within expert guidance and that are not restricted per protocol (see Section 3.8) are allowed in order to accommodate local standards of care.

1.3 Benefit/risk and ethical assessment

There are few treatment options for patients whose asthma remains uncontrolled on medium to high-dose ICS-LABA (GINA 2014). The evidence base for oral add-on therapies (ie, oral corticosteroids, leukotriene inhibitors, and xanthenes) is extremely limited. Anti-IgE therapy (ie, omalizumab) may improve control in patients with severe asthma and IgE-mediated allergy to a perennial allergen. Tiotropium is a long-acting bronchodilator that has recently been shown to produce improvement in lung function and exacerbation risk (pooled data) in patients with severe asthma, with inconsistent effects on other measures of asthma control (Kerstjens et al 2012). As such, new therapies are needed for asthma management in patients who remain uncontrolled on standard of care.

In adult patients whose asthma was poorly controlled on medium-to-high dose ICS-LABA benralizumab, at fixed doses of ≥20 mg, produced improvements in multiple metrics of asthma control including the annual rate of asthma exacerbations, lung function, ACQ-6 scores, and symptoms (Castro et al 2014). These findings have subsequently been confirmed in two large Phase 3 studies (Bleecker et al 2016, FitzGerald et al) where a fixed dose of 30 mg was given either every 4 weeks or every 8 weeks. Clinical benefit appeared to be greatest in patients with blood eosinophil counts ≥300/µL. The blood eosinophil count below which

benralizumab is generally not effective remains unclear at this point in time, and will be explored in this study.

Development of anti-drug antibodies (ADA) to benralizumab has been documented. Theoretical risks of developing ADA include decreased drug efficacy and hypersensitivity reactions (e.g., anaphylaxis or immune complex disease). There was no apparent impact of ADA on overall benralizumab safety or efficacy in the previous Phase 3 studies in asthma. Serious hypersensitivity reactions (including anaphylaxis) are an identified risk of biologic therapy, including benralizumab. Anaphylaxis may be life-threatening. Risk minimization includes observation in line with clinical practice at the clinical site following IP administration for the appearance of any acute drug reactions.

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 (IB).

1.4 Study Design

This is a randomised, double-blind, parallel group, placebo-controlled study designed to evaluate the efficacy and safety of a fixed 30 mg dose of benralizumab administered subcutaneously for patients with a history of asthma exacerbations and uncontrolled asthma receiving medium to high-dose inhaled corticosteroid plus long-acting β_2-agonist (ICS-LABA) with or without oral corticosteroids and additional asthma controllers. Approximately 666 patients are expected to be randomised in the study with at least 70% patients to be randomised from China. Patients will be stratified by country/region, age group (adult or adolescent), and peripheral blood eosinophil count at time of Visit 1 (<300 or ≥300 cells/μL).

All the patients will be randomised to either placebo or benralizumab, every 4 weeks for the first 3 doses and then every 8 weeks thereafter.

Strata closure process:

1 The eosinophil <300/µL stratum will be closed to the patients from the China when the total number of Chinese patients in the stratum reaches approximately 166.

2 The eosinophil <300/µL stratum will be closed to the patients from all countries when the total number of patients in the eosinophil <300/µL stratum reaches approximately 222.

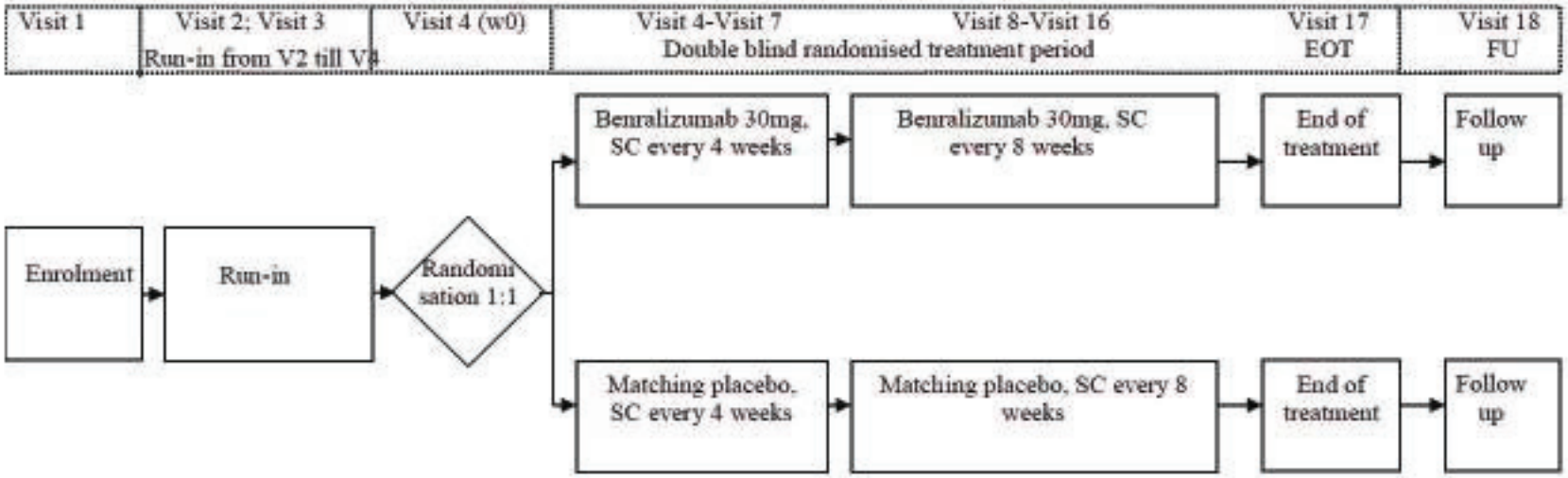
3 The whole study will be closed for recruitment when the total number of patients in the eosinophil ≥300/µL stratum reaches approximately 444, with at least 70% Chinese patients in the stratum.

After initial enrolment and confirmation of entry criteria, patients will proceed to the run-in period of a minimum 4 weeks to allow adequate time for all of the eligibility criteria to be evaluated (Figure 1). Patients who meet eligibility criteria will be randomised to a 48-week treatment period. Patients will be maintained on their currently prescribed medium to high-dose ICS- LABA therapy and other asthma controllers, without change, from visit 1 until the end of the study.

A follow-up visit will be conducted at Week 56.

Figure 1 Study flow chart

Dosing regimen: Every 4 weeks for first 3 doses, then every 8 weeks thereafter.



2. STUDY OBJECTIVES

2.1 Primary Objective

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

a For the purpose of the protocol, worsening of asthma is defined as new or increased symptoms and/or signs (examination or lung function) that can be either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (diary-driven). The ePRO device will be programmed to alert both the patient and study centre when certain pre-specified worsening thresholds are crossed including: decrease in morning peak flow ≥30% on at least 2 of 3 successive days compared with baseline (last 10 days of run-in), and/or a ≥50% increase in rescue medication or 1 new or additional nebulized β_2 agonist on at least 2 of 3 successive days compared with the average use for the previous week and/or nocturnal awakening due to asthma requiring rescue medication use for at least 2 of 3 successive nights, and/or; an increase in total asthma symptom score (the sum of day time [evening assessment] and night time [morning assessment] of at least 2 units above the run-in average (last 10 days of run-in), or the highest possible score (daily score of 6), on at least 2 of 3 successive days.

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

2.2 Secondary Objectives

Secondary Objectives:	**Outcome Measure:**
To assess the effect of benralizumab on pulmonary function	Pre-bronchodilator FEV_1[b]
To assess the effect of benralizumab on asthma symptoms and other asthma control metrics (as per the ePRO)	• Asthma symptom score (total[b], daytime, and night time) • Rescue medication use • Home lung function (morning and evening Peak expiratory flow (PEF)) • Nights with awakening due to asthma • Asthma Control Questionnaire 6 (ACQ-6)
To assess the effect of benralizumab on other parameters associated with asthma exacerbations	Time to first asthma exacerbation and proportion of patients with ≥1 asthma exacerbation
To assess the effect of benralizumab on health-related quality of life	St. George's Respiratory Questionnaire (SGRQ)
To assess the effect of benralizumab on emergency room/urgent care visits and hospitalizations due to asthma	Annual rate of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalization
To evaluate the effect of benralizumab on health care resource utilization	• Asthma specific resource utilization (eg, unscheduled physician visits, use of other asthma medications)
To characterize the pharmacokinetics and immunogenicity of benralizumab	• Serum trough concentrations • Incidence of anti-drug antibodies (ADA) and neutralizing antibodies (nAb), ADA titer
To assess the impact of benralizumab on blood eosinophil levels	• Blood eosinophils

b Key secondary efficacy endpoints

2.3 Safety Objective

Safety Objective:	**Outcome Measure:**
To assess the safety and tolerability of benralizumab	• AE/SAE • Laboratory variables • Electrocardiogram ECG • Vital Signs

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

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.

3.1 Inclusion criteria*

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

1 Written informed consent, and assent when applicable for study participation must be obtained prior to any study related procedures being performed (local regulations are to be followed in determining the assent/consent requirements for children and parent[s]/guardian[s]) and according to international guidelines and/or applicable local guidelines.

2 Female and male aged 12 to 75 years, inclusively, at the time of Visit 1

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

3 Women of childbearing potential (WOCBP) must agree to use a highly effective method of birth control (confirmed by the Investigator) from enrolment, throughout the study duration and within 12 weeks after last dose of IP and have negative serum pregnancy test result on Visit 1. Highly effective methods (those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation- oral, intravaginal, or transdermal; progestogen-only hormonal contraception associated with inhibition of ovulation- oral, injectable, or implantable; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; sexual abstinence, i.e. refraining from heterosexual intercourse (The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient); vasectomized sexual partner provided that partner is the sole sexual partner of the WOCBP study patient and that the vasectomized partner has received medical assessment of the surgical success.

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 randomisation 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. Until FSH is documented to be within menopausal range treat the patient as WOCBP.

– 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 Weight of ≥40 kg.

5 History of physician-diagnosed asthma requiring treatment with medium-to-high dose ICS (>250µg fluticasone propionate dry powder formulation equivalents total daily dose) and a LABA, for at least 6 months prior to Visit 1. Equivalents for fluticasone propionate dry powder can be found in Appendix E.

Documented treatment with medium to high dose ICS and a LABA for at least 3 months prior to Visit 1 with or without oral corticosteroids and additional asthma controllers. The ICS and LABA can be part of a combination product or given by separate inhalers. Equivalents for fluticasone propionate dry powder can be found in Appendix E.

The ICS dose must be ≥500 mcg/day fluticasone propionate dry powder formulation or equivalent daily. For ICS/LABA combination preparations, the highest approved maintenance dose in the local country will meet this ICS criterion.

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

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

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

8 Documented post-bronchodilator (post-BD) reversibility in FEV1 of ≥12% and ≥200 mL in FEV1 within 12 months prior to Visit 1. If historical documentation is not available, reversibility must be demonstrated and documented at Visit 2.

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

10 Fulfilment of at least 1 of the following conditions over the 7 days prior to randomisation:

– >2 days with a daytime or night time symptoms score >1

- Rescue SABA use on >2 days
- ≥1 nocturnal awakening due to asthma

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

12 At least 70% compliance with usual asthma controller ICS-LABA during over the 14 days prior to randomisation based on Asthma Daily Diary. Patients who experience an asthma exacerbation during run-in may temporarily be unable to complete their diary due to illness or hospitalization. In these cases, ICS-LABA compliance will be calculated for the period after systemic corticosteroid therapy is complete.

13 At least 70% compliance with ePRO completion

- At least 70% compliance defined as completing Asthma Daily Diary for any 10 complete days (i.e., consecutive evening and morning, for example, Day -14 evening + Day -13 morning) of the last 14 days of the run-in period.

14 Pre-bronchodilator (Pre-BD) FEV1 of <80% predicted (<90% predicted for patients aged 12 to 17 years) at Visit 2.

15 ACQ-6 score ≥ 1.5 at Visit 2.

*: No.1 to No. 8, No.14 and No.15 are the inclusion criteria at screening; No. 9 to No.13 are the inclusion criteria at randomisation.

3.2 Exclusion criteria

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

1 Known history of clinically important pulmonary disease other than asthma (e.g., 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 (e.g., allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).

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

Affect the safety of the patient throughout the study

Influence the findings of the studies or their interpretations

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

3 Known history of allergy or reaction to the investigational product (IP) formulation.

4 Known history of anaphylaxis to any biologic therapy.

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

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

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

8 Known history of any clinically significant cardiac disease (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, myocardial infarction) or any ECG abnormality obtained during the screening period, which in the opinion of the investigator may put the patient at risk or interfere with study assessments.

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

10 Current active liver disease.
Chronic stable hepatitis B and C (including positive testing for hepatitis B surface antigen (HBsAg) or hepatitis C antibody), or other stable chronic liver disease are acceptable if subject otherwise meets eligibility criteria. Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.

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

12 Current smokers at Visit 1 are not allowed. Former smokers with smoking history ≥ 10 pack-years at Visit 1 are not allowed; Former smokers with a smoking history of <10 pack years must have stopped for at least 6 months to be eligible.

13 Known history of cancer:

- Patients who have had basal cell carcinoma, localized squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent, and assent when applicable was obtained.
- Patients who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years

prior to the date informed consent, and assent when applicable, was obtained.

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

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

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

17 Receipt of live attenuated vaccines 30 days prior to the date of randomisation.

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

18 Receipt of any investigational nonbiologic within 30 days or 5 half-lives prior to randomisation, whichever is longer. Use of any off-label medications, for example medications locally approved for Chronic Obstructive Pulmonary Disease but not for asthma, are also not allowed from 30 days prior to visit 1 and throughout the study.

19 Previously randomised in any benralizumab (MEDI-563) study, including the present study.

20 Initiation of new allergen immunotherapy is not allowed within 30 days prior to the date of informed consent, and assent when applicable. 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.

21 Current use of any oral or ophthalmic non-selective β-adrenergic antagonist (e.g., propranolol).

22 Planned surgical procedures during the conduct of the study.

23 Currently breastfeeding or lactating women.

24 Current participation in another clinical investigational study.

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

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

27 Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level >3 times the upper limit of normal (ULN), confirmed by repeated testing during screening period.

Transient increase of AST/ALT level that resolves by the time of randomisation is acceptable if in the Investigator's opinion the subject does not have an active liver disease and meets other eligibility criteria.
Note: The patients previously screen failed in this study due to this criterion are allowed to be rescreened if they meet this updated criterion.

28 Five-lipoxygenase inhibitors (e.g., Zileuton) and roflumilast are prohibited.

29 Received bronchial thermoplasty (BT) as treatment of asthma within 12 months prior to Visit 1.

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

3.3 Patient enrolment and randomisation

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 or designee will:

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

2 Assign each potential patient a unique enrolment number, beginning with 'E#' via interactive web/voice response system (IWRS/IVRS).

3 Determine patient's eligibility.

4 Assign eligible patient unique randomisation code via IWRS/IVRS.

Patients will be allocated to receive benralizumab or placebo in a 1:1 ratio. The randomisation will be stratified by country/region, age group (adult or adolescent), and blood eosinophil count at Visit 1 (≥300/µL or <300/µL) and the randomisation numbers will be grouped in blocks. The <300/µL stratum will be closed when the total number of patients in the stratum hits approximately 222. When a stratum is full, patients who fall within that stratum will not be randomised and will be withdrawn from the study (see Section 3.10.2).

Randomised patients, who discontinue from IP or withdraw from study, will not be replaced. If a patient withdraws from the study, then his/her enrolment number/randomisation code cannot be reused.

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

3.4 Procedures for handling incorrectly randomised patients

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

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the patient from treatment. Study treatment must be discontinued in cases where continued treatment is deemed to pose a safety risk to the patient. In those cases where continuation of the study treatment is judged not to present a concern related to safety and disease management, the rationale for continuing study treatment must be clearly documented. Regardless of what is decided about continuation of IP or not, all randomised subjects should be encouraged to remain in the study and continue to be followed up in accordance with defined study procedures. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Randomisation codes will be assigned strictly sequentially in each stratum as patients become eligible for randomisation. The randomisation code will be assigned from a randomisation list prepared by a computerized system provided by Parexel Informatics on behalf of AZ (AZRand).

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

3.6 Methods for ensuring blinding

The study is a double-blind study. AstraZeneca staff involved in the study, the patients, and the investigators/site staff involved in the treatment of the patients or in their clinical evaluation will not be aware of the treatment allocation.

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

As PK sample will be analysed only for patients receiving benralizumab, treatment data (randomization list and kit list) will be available to bioanalytical lab personnel for PK sample analysis during the conduct of study. The bioanalytical lab personnel, are independent of the study team and sites, will not engage in study activities other than PK/immunogenicity sample

analysis. The treatment data will only be sent to the lab scientist and will be restricted within the lab scientist and analysts. The information in the randomization and kit list will be kept from other personnel involved in the conduct of the study and any CRO handling data until study unblinding.

Maintaining the blinding to the patient's blood eosinophil counts

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

- From Visit 4 on, eosinophil, basophil or monocyte count will be redacted from central laboratory reports to prevent the Principal Investigator/designee from possibly deducing the 'eosinophil + basophil' contribution to the complete blood count. In cases where the Investigator requires an eosinophil, basophil or monocyte count for managing safety issues, AstraZeneca physician should be notified of all such cases, without being revealed the eosinophil, basophil or monocyte count.
- Regarding lab results obtained during the treatment period but ordered outside of the clinical trial, centre staff who are directly involved in the patient's treatment and evaluation should remain blinded to any eosinophil, basophil and monocyte results included as part of outside lab reports.
- If the Investigator have to order any local safety laboratory assessments to follow up patient's safety, the requested tests should be restricted to the question at hand. For example, if a haemoglobin is desired the Investigator should avoid ordering a complete blood cell count with differential.

3.7 Methods for unblinding

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

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

3.8 Restrictions

3.8.1 Asthma medication restrictions

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

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

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

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

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

(b) **Use of short acting anticholinergics** (e.g., 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** (e.g., 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, should be continued unchanged from visit 1until the end of study.

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

Changes to the patient's background controller regimen are discouraged during the treatment period, unless judged medically necessary by the Investigator. All changes in the patient's background medication should be discussed beforehand with the AstraZeneca study physician and documented in source 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 centre at scheduled visits (see Table 1 and Table 2). Restrictions to patient's background medication are required prior to the spirometry as described below (also see Section 5.1.2):

Screening Visit 2: Patients should withhold their usual ICS, LABA, Long-acting anti-muscarinic (LAMA), LTRA or theophylline medications on the morning of the FEV_1 measurement and reversibility test. Twice daily ICS- LABA therapies should be withheld for 12- 24 hours; once daily therapies containing ICS, LABA, LAMA, LTRA, theophylline therapies should be withheld for ≥24 hours for eligibility assessment (see Section 3.1, inclusion criterion 7).

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

Treatment Visits 4-17: Patients should withhold their usual ICS, LABA, LAMA, LTRA or theophylline medications on the morning of the scheduled spirometry. Twice daily ICS-LABA therapies should be withheld for 12- 24 hours; once daily therapies containing ICS, LABA, LAMA, LTRA or theophylline therapies should be withheld for ≥24 hours prior to the spirometry assessment. This is especially important prior to scheduled spirometry assessments (see Table 2) in order to maintain the integrity of planned efficacy analyses around lung function improvement. In addition, SABA should not be used within 6 hours prior to the spirometry assessments. The patient's usual asthma controller medications may be administered following completion of the pre-BD spirograms. The suggested order of administration of the patient's usual asthma controller and IP administration relative to scheduled pre -BD spirometry is given in Section 5.1.2.

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

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

1 Remain at the centre until such time that the 6 hour withholding time has been reached if it does not exceed the 1.5 hour spirometry window, or
2 Return on another day, within the visit window.

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

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

(g) Asthma medication restrictions on unscheduled visits

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

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

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

3.8.2 Other medication restrictions

(a) Use of immunosuppressive medication (other than prior, stable oral corticosteroid for the maintenance treatment of asthma) is not allowed. Topical administration of immunosuppressive medication may be allowed at the discretion of the Investigator after discussion with the AstraZeneca study physician. Please see Section 3.2 exclusion criterion 14 for examples and further details.

(b) Receipt of live attenuated vaccines within 30 days prior to randomisation, during the treatment period, and for 12 weeks after the last dose of the IP is not allowed.

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

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

Five-lipoxygenase inhibitors (e.g., Zileuton)

Roflumilast

Oral or ophthalmic non-selective β-adrenergic antagonist (eg, propranolol).

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

3.8.3 Other restrictions

(a) Fertile and sexually active female patients should use effective contraceptive methods throughout the study and at least for 12 weeks after last administration of the IP. (see Section 3.1, inclusion criterion 3 and Section 6.6).

(b) Patients must abstain from donating blood, plasma from the time of informed consent, and assent when applicable, and for 12 weeks after last dose of IP.

3.9 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

1 Patient decision. Patients are free to discontinue treatment at any time, without prejudice to further treatment (see Section 3.10).

2 Adverse event (AE) that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing.

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

4 Severe non-compliance to study protocol.

5 Eligibility requirement found not to be fulfilled (see section 3.4).

6 Pregnancy.

7 Lost to follow-up[1].

8 Development of any study specific criteria for discontinuation:
- Anaphylactic reaction to the IP requiring administration of epinephrine.
- Development of helminth parasitic infestations requiring hospitalization.
- An asthma-related event requiring mechanical ventilation.

If a patient misses more than 2 doses of IP at any time within a calendar year, it is strongly recommended that a conversation between the investigator and AZ study physician takes place to review the patient's adherence to treatment and decide on further patient's disposition.

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments – see Section 3.10), without prejudice to

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

further treatment. A patient that decides to discontinue investigational drug will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Reasons for premature discontinuation of IP should be recorded in the eCRF.

All patients who prematurely discontinue IP should return to the study centre and complete the procedures described for the Premature IP Discontinuation visit (IPD) within 8 weeks +7 days after the last dose of IP. At that visit, patients should be encouraged to remain in the study to complete all subsequent study visits, procedures and assessments or alternatively agree to be contacted by phone calls at monthly intervals in order to collect AEs/SAEs, changes in concomitant medication, health care utilisation, and asthma exacerbation information.

If a patient is withdrawn from study, see Section 3.10. Patients not willing to continue to participate in the study should return to the study centre 1 last time within16 weeks ±7 days after the last dose of IP for final study related assessments, ePRO devices if applicable (e.g., for patient reported outcomes) and all study drugs should be returned by the patient. Any AEs that are unresolved at the end of study will be followed up by the Investigator for as long as medically indicated, but without further recording in the CRF (See Section 6).

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded in eCRF as ‘Screen failure’ (the potential patient who does not meet one or more criteria required for participation in a trial, this reason for study withdrawal is only valid for not randomised patients). No further study related follow-up of these patients is required.

‘Failure to meet randomisation criteria’ should be selected for an indication that the patient has been unable to fulfil/satisfy the criteria required for assignment into a randomised group (it is only applicable for patient found not meeting criteria after randomisation).

3.10.2 Withdrawal due to recruitment completion in a randomisation stratum

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

Strata closure process:

1 The eosinophil <300/μL stratum will be closed to all the patients from China when the total number of Chinese patients in the stratum reaches approximately 166.

2 The eosinophil <300/μL stratum will be closed to the patients from all countries when the total number of patients in the stratum reaches approximately 222.

3 The whole study will be closed for recruitment when the total number of patients in the eosinophil ≥300/μL stratum reaches approximately 444, with at least 70% Chinese patients in the stratum.

3.10.3 Withdrawal of the informed consent/assent

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

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

If patient agrees, he/she will be asked to return to the study centre and complete procedures described for the IPD (Premature IP Discontinuation) visit. For patients who are not willing to continue to participate in the study, he/she will complete IPD within 8 weeks +7 days after the last dose of IP and Follow-up visit within 16 weeks ±7 days after the last dose of IP.

3.10.4 Withdrawal of informed consent/assent for donated biological samples

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

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

The Principal Investigator or designee:

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

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

3.10.5 Withdrawal due to repeat exacerbations during screening

Patients who experience more than 1 asthma exacerbation between Visit 1 and Visit 4 will not be randomised and will be withdrawn from the study (see Section 4.1.3.1).

The start of an exacerbation is defined as the start date of systemic corticosteroids, or the start date of a temporary increase in a stable oral corticosteroid background dose, or that start date of hospital admission, whichever occurs earlier. The end date is defined as the last day of systemic corticosteroids or the last day of a temporary increase in a stable oral corticosteroid background dose, or the date of discharge from a hospital, whichever occurs later (see Section 8.4.1.1).

Patients who are diagnosed with an asthma exacerbation at Visit 4 will not be randomised and will be withdrawn from the study (see Section 4.1.3.1).

The reason of the withdrawal should be documented in the source and eCRF as 'Development of study-specific withdrawal criteria'.

Patients who are withdrawn due to exacerbation at Visit 4 or due to exacerbations between Visit 1 and Visit 4 may be re-screened twice (see Section 4.1.3.1).

3.11 Discontinuation of the study

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

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

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

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

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan – Screening period

Assessment/ activity	Refer to	Enrolment	Run-in	
		V1 (w –6)	V2 [a] (w –5)	V3 [b] (≤w –1)
		Visit window (days)		
		28-42 days [c]		
Informed consent/assent	10.4	X		
Inclusion/exclusion criteria	3.1/3.2	X	X	X
Medical and asthma history	4.1	X		
Complete physical examination	5.2.1.1	X		
Weight, Height	5.3.1	X		
Vital Signs	5.2.2	X		X
Local ECG	5.2.3	X		X
Serum chemistry	5.2.4	X		X
Haematology	5.2.4	X		X
Urinalysis	5.2.4	X		X
Serology (hepatitis B,C)	5.3.4.1	X		
Serum pregnancy test [d]	5.2.4.1	X		
FSH [e]	5.2.4.1	X		
Screening reversibility [f]	5.1.2.1		X	
Home PEF testing	5.1.3		X	X
Asthma Daily Diary adherence	5.3.2.1		X	X
Health care resource utilization	5.3.3	X		
Pre- BD, Spirometry	5.1.2		X	

Table 1 Study Plan – Screening period

Assessment/ activity	Refer to	Enrolment	Run-in	
		V1 (w –6)	V2 [a] (w –5)	V3 [b] (≤w –1)
		Visit window (days)		
		28-42 days [c]		
Adverse events	6.1	X	X	X
Concomitant medication	7.6	X	X	X
ACQ-6			X	

a. Visit 2 may take place as soon as medication restrictions prior to spirometry/reversibility tests are met (see Section 3.8) and should occur no later than 1 week after Visit 1. Visit 2 procedures may be performed on the same day as Visit 1 if the medication restriction is met.
b. 'Visit 3 and Visit 4 may take place on the same day only for well characterized patients (those who did not have lab results outside the normal range at Visit 1 for parameters associated with eligibility criteria (eg Liver Function Tests)) as any such results should be retested, with results available before randomisation, in order to ensure patient eligibility is not affected.'
c. Not applicable for patients with exacerbation during screening period (see Section 4.1.3.1).
d. Serum Beta- human chorionic gonadotropin (beta-HCG) to be done in all females at screening Visit 1 except for those who are NOT of child bearing potential as defined in inclusion criterion 3. This test is to be sent to and analysed at the central laboratory.
e. FSH test done only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 months.
f. When historical proof of post-BD (post-BD) reversibility in FEV_1 is documented within 12 months prior to Visit 1, the screening reversibility does not need to be performed, otherwise the test to be performed on Visit 2. If a patient fails the protocol-specified reversibility criterion, a second attempt is allowed. Re-test can be done only once, not earlier than next calendar day and not later than 7 calendar days after the failed attempt.

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

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

Assessment/ activity	Refer to	R	Treatment												EOT	IPD	FU [f]	UNS [g]
		V4	V5 phone	V6	V7	V8 phone	V9	V10 phone	V11	V12 phone	V13	V14 phone	V15	V16 phone	V17		V18	
		w0	w0D6	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48		w56	
		Visit window (days) [a]																
		±0	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	±7	N/A
Inclusion/exclusion criteria	3.1/3.2	X																
Complete physical examination	5.2.1.1	X													X	X		X
Brief physical examination	5.2.1.2			X	X		X		X		X		X					
Weight	5.3.1	X							X						X	X		
Height (Only for adolescents)	5.3.1														X	X		
Vital Signs	5.2.2	X		X	X		X		X		X		X		X	X		X
Local ECG	5.2.3								X						X	X		
Serum chemistry	5.2.4			X	X				X				X		X	X		
Haematology	5.2.4			X	X				X				X		X	X	X[b]	
Urinalysis	5.2.4			X	X				X				X		X	X		
Urine pregnancy test [c]	5.2.4.1	X		X	X		X		X		X		X		X	X		
PK	5.3.5	X*							X*						X	X		
ADA/nAb [d]	5.3.6	X*							X*						X	X		
Home PEF adherence	5.1.3	X		X	X	X	X	X	X	X	X	X	X	X	X	X		

Assessment/ activity	Refer to	R	Treatment												EOT	IPD	FU [f]	UNS [g]
		V4	V5 phone	V6	V7	V8 phone	V9	V10 phone	V11	V12 phone	V13	V14 phone	V15	V16 phone	V17		V18	
		w0	w0D6	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48		w56	
		Visit window (days) [a]																
		±0	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	±7	N/A
Asthma Daily Diary adherence	5.3.2.1	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
ACQ-6 adherence	5.3.2.2	X		X	X		X		X		X		X		X	X		
SGRQ adherence	5.3.2.3	X			X		X		X		X		X		X	X		
Health care resource utilization	5.3.3			X	X	X	X	X	X	X	X	X	X	X	X	X		
Assessment of asthma exacerbations	5.1.1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pre- BD, spirometry	5.1.2	X		X	X		X		X		X		X		X	X		
Randomisation	4.2	X																
Administration of IP [e]	7.4	X		X	X		X		X		X		X					
Adverse events	6.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	7.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. All visits are to be scheduled from the date of randomisation but not from the date of previous visit
b. Eosinophil count to be measured only
c. For all females except those NOT of child bearing potential as defined in inclusion criterion 3, urine HCG test to be done at study sites on each clinic visit before IP administration
d. All ADA positive samples will be tested for neutralizing antibodies (nAb).
e. In case of anaphylaxis additional samples to be taken (see Section 7.7)
f. Patients that complete the 48-week double blind randomised treatment period will have a final follow-up visit at Week 56, Visit 18

g. Unscheduled visits may be initiated as needed. Adverse event, concomitant medication and assessment of asthma exacerbation are mandatory, and additional assessments may be performed at these visits, at the discretion of the Investigator.

h. Pre-dose sample

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

4.1 Screening period

4.1.1 Enrolment (Visit 1)

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

Patient must sign the Informed Consent Form (ICF) prior to any other Visit 1 procedures.

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.

Source documentation is required for physician-diagnosed asthma, ICS-LABA use (Section 3.1, criterion 5) and asthma exacerbations over the prior year (Section 3.1, criterion 7) . A patient verbal history suggestive of asthma symptoms and/or prior asthma exacerbations, but without supporting documentation, is not sufficient to satisfy these inclusion criteria.

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

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

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

Central laboratory tests for absolute blood eosinophil count will be performed at Visit 1 . Patients who have a blood eosinophil count of <300 but ≥150/μL at Visit 1 can be re-tested once. It is recommended that any re-test for blood eosinophils is performed not earlier than 4 weeks from the previous testing; in case of recent treatment with systemic corticosteroids, an interval of ≥6 weeks from the last dose is recommended.

4.1.2 Run-in (Visit 2, Visit 3)

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

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

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

Visit 2 may take place as soon as medication restrictions prior to spirometry/reversibility tests are met (see Section 3.8) and should occur no later than 1 week after Visit 1. Visit 2 procedures may be performed on the same day as Visit 1 if the medication restriction is met. If Visit 2 procedures are actually planned at Visit 1 as a convenience, then the ICF must be signed prior to instructing the patient to withhold any medication.

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

Note: In cases when historical proof of post-BD reversibility in FEV_1 (see inclusion criterion 8) is documented within 12 months prior to Visit 1, the screening reversibility does not need to be performed (see Section 5.1.2.1)

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

Visit 3 can be performed within 1 week before Visit 4. Visit 3 and Visit 4 may take place on the same day only for well characterized patients (those who did not have lab results outside the normal range at Visit 1 for parameters associated with eligibility criteria (e.g. Liver Function Tests)) as any such results should be retested, with results available before randomisation, in order to ensure patient eligibility is not affected. On Visit 4 ACQ-6 will be recorded (for baseline purposes only). Patient's eligibility should be evaluated at each visit during the run-in period with the relevant documentation entered in the source and eCRF.

4.1.3 Re-screening

Re-screening may be allowed twice for the patient screen-failed due to asthma exacerbation, otherwise re-screening is only allowed once.

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

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

Re-screening and/or up to 14-day extension of screening period is allowed for transient reasons (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits). These cases should be discussed with the AstraZeneca study physician and documented in the Investigator Study File (ISF).

For those patients who were screen failed at Visit 3 or thereafter the re-screening period can be reduced. Visit 1 and Visit 2 can be done at the same day; Visit 3 can be done 1 week after Visit 2, and Visit 4 can be done 1 week after Visit 3.

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

A second re-screening may be allowed only when the screen failure reason was asthma exacerbation. All the cases should be discussed with the AstraZeneca study physician and documented in the Investigator Study File (ISF).

4.1.3.1 Procedures for Patients Who Experience an Exacerbation during Screening

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

- **Exacerbations Between Visit 1 and Visit 3:**
  - The next regular study visit (Visit 2 or Visit 3) will be delayed and may proceed no sooner than 14 days after the last dose of systemic steroids.
  - For patients on chronic oral steroid therapy, Visit 2 or Visit 3 can commence minimal 14 days after the daily dose has returned to the pre-exacerbation baseline level.
- **Exacerbations Between Visit 3 and Visit 4:**
  - Visit 4 will be delayed. Patients will return to the centre for an unscheduled visit at the time their systemic steroid regimen is complete or the dose has returned to baseline.
  - Central laboratory safety assessments will be collected (see Table 3) at the unscheduled visit and checked by the Investigator prior to randomisation.

  - Randomisation at Visit 4 can commence minimal 14 days after the systemic steroid regimen is complete or the dose has returned to baseline.

- **Exacerbations at Visit 4:**
  - Patients who are diagnosed with an asthma exacerbation at Visit 4 should be screen-failed.

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

Patients who are screen-failed with an exacerbation at Visit 4 or due to exacerbation between Visit 1 and Visit 4 may be re-screened 2 times.

4.2 Treatment period

Inclusion criteria at randomisation will be confirmed at Visit 4. Before randomisation the patient's compliance with usual asthma controller ICS-LABA and ePRO completion must be confirmed (see Section 3.1, inclusion criterion 12 and 13).

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

Adult or adolescent patients will be randomised to either placebo or benralizumab.

The first dose of the IP will be administered at Visit 4 after the patient's randomisation via IWRS/IVRS. During Visit 4, but before the first dose of IP, the patient should complete the following PRO assessments on the ePRO device: SGRQ and ACQ-6.

For Visits 6 -16 spirometry and blood sampling (for hematology, serum chemistry, PK, ADA/nAb) may be performed 1 day prior to the scheduled date of IP injection, at the discretion of the Investigator. All other study procedures (except ACQ-6) must be done on the scheduled day of IP injection. Urine pregnancy tests must be done on injection days, prior to IP administration.

Following randomisation the patient will receive 48-week double-blind treatment, with the last dose of benralizumab/placebo administered at Visit 15 (Week 40). Patients will have scheduled visits or phone call at 4-week interval to complete protocol-specific assessments and IP administration, as listed in Table 2. Restrictions as set out in Section 3.8 will continue to apply throughout the treatment period. In case of asthma worsening/exacerbation (see Section 5.1.1), patients should be evaluated at the study centre, when feasible, at an unscheduled visit, or ordinary visit if the worsening happens to fall within a scheduled visit window.

Patients will continue to monitor lung function at home, as well as record asthma symptoms and responses to questionnaires using ePRO device throughout the 48-week treatment period (see Section 5.3.2 for details).

At Week 48 patients will come to the centre for the End of Treatment (EOT) visit.

Patients who prematurely discontinued IP (see Section 3.9) and are not willing to continue to participation in the study should return to the study centre and complete procedures described for the IPD visit (Premature IP Discontinuation) within 8 weeks +7 days after the last dose of IP and Follow-up visit within 16 weeks ±7 days after the last dose of IP, respectively.

Patients will return the ePRO device on EOT or IPD visit (for patients who are not willing to continue to participation in the study).

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

4.3 Follow-up period

All the patients will return at Week 56 for a final Follow-Up visit.

4.4 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the patient's ability to conduct the study. The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with Good Clinical Practice, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the Informed Consent Form (ICF) should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.
- Home or Remote visit: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).

- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home Investigational Product (IP) administration: Performed by a site qualified HCP, HCP provided by a TPV, or by the patients or the patient's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix G.

5. STUDY ASSESSMENTS AND PROCEDURES

5.1 Efficacy assessments

5.1.1 Assessment of asthma exacerbations

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

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

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

- Decrease in morning peak flow ≥30% on at least 2 of 3 successive days compared with baseline (last 10 days of run-in), and/or
- A ≥50% increase in rescue medication on at least 2 of 3 successive days compared with the average use for the previous week, and/or use of 1 new or additional nebulized β2 agonist on at least 2 of 3 successive days compared with the average use for the previous week, and/or
- Nocturnal awakening due to asthma requiring rescue medication use for at least 2 of 3 successive nights, and/or
- An increase in total asthma symptom score (the sum of day time [evening assessment] and night time [morning assessment] of at least 2 units above the run-in average (last 10 days of run-in), or the highest possible score (daily score of 6), on at least 2 of 3 successive days

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

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

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

Reasonable attempts should be made by the Investigator to bring the patient into the study centre for evaluation of a diary alert or patient initiated asthma worsening, particularly when it results in additional treatment being prescribed. Study centre evaluations for asthma worsening may occur as an unscheduled visit or as part of an ordinary centre visit if the worsening happens to be coincident with a scheduled visit window. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study centres (eg, by the primary care HCP or at an emergency department/hospital) and details entered into the exacerbation eCRF in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the appropriate module of the eCRF.

5.1.2 Spirometry

General requirements

Lung function (FEV_1 and Forced vital capacity (FVC)) at the study centre will be measured by spirometry using equipment provided by central vendor. Spirometry will be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005).

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

Important! Patients should withhold their usual ICS-LABA, LAMA, LTRA or theophylline medications on the morning of the screening FEV1 measurement, reversibility test (see Section 3.1, inclusion criterion 8 and 11), and all scheduled spirometry visits. Twice daily ICS- LABA therapies should be withheld for 12- 24 hours; once daily therapies containing ICS, LABA, LAMA, LTRA or theophylline therapies should be withheld for ≥24 hours before scheduled centre visit spirometry as this will affect the pre-BD FEV_1 value; they may be taken subsequently, at the centre. For the same reason patients should not use their rescue SABA medication (albuterol, salbutamol or levalbuterol) within 6 hours of a scheduled centre 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 3.8.

Time of day for scheduled centre visit spirometry

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

Spirometry technique

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

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

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

Post-bronchodilator spirometry

Post-BD spirometry will be performed to satisfy reversibility inclusion criterion 8 (for patients without prior documentation of reversibility) as listed in Table 2. The post BD spirometry

procedures should commence according to the regimen for reversibility testing outlined in Section 5.1.2.1.

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

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

Record keeping

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

Spirometry references

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

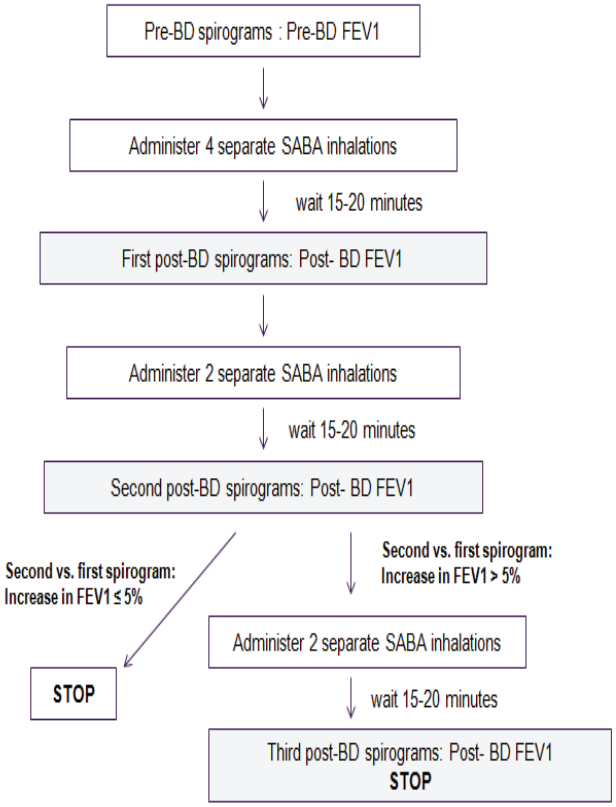
FEV_1 expressed as percent of the PN value will be calculated as follows:

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

5.1.2.1 Reversibility test

The procedure described in this section refers to the reversibility testing at Visit 2 (to evaluate inclusion criterion 8, if applicable). Maximal bronchodilatation should 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 (Sorkness et al 2008). 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 3.8)
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 Following this, an additional 2 inhalations of albuterol, salbutamol or levalbuterol should be administered as single inhalations, 30 seconds apart (for a total of 6 inhalations). Second post-BD spirometry should be performed 15-20 minutes later.
4 If the incremental change in FEV_1 after 6 inhalations of albuterol, salbutamol or levelbuterol is ≤5% of the FEV_1 value after 4 inhalations, the procedure is complete. If the change is >5% an additional 2 inhalations of albuterol, salbutamol or levalbuterol should be administered in single inhalation 30 seconds apart and a third and final post-BD spirometry should be performed 15-20 minutes later.

A lower total dose, eg, 2 inhalations instead of 4 in the first round of puffs, and/or a total of less than 8 puffs, can be used if there is a concern about any effect on the patient's heart rate, tremor or safety. For the visit 2 reversibility testing, it is acceptable to stop the procedure when the eligibility criterion is met. If a reversibility maneuver that meets inclusion criteria (≥12% and ≥200 mL) is rejected as the best maneuver after central revision, it may still be used to satisfy Inclusion Criterion 8.

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

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

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

Reversibility is calculated as follows:

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

Note: In cases when historical proof of post-BD (post-BD) reversibility in FEV_1 (see inclusion criterion 7) is documented within 12 months prior to Visit 1 the screening reversibility test does not need to be performed.

5.1.3 Home peak expiratory flow testing

An electronic, hand-held spirometer (peak flow meter) will be dispensed to the patient on Visit 2 (after respiratory inclusion criteria have been confirmed, see Section 3.1, criterion 8 and 11).

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 peak expiratory flow should start from the evening of Visit 2 until the morning of Visit 17 using an ePRO device. When possible, ambulatory lung function measurements should be taken at least 6 hours after the last dose of SABA rescue medication.

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

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

5.2 Safety assessments

5.2.1 Physical examination

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

Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, as compared to the data collected at Visit 1, will be reported as an AE as described in Section 6.1.

5.2.1.1 Complete physical examination

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

5.2.1.2 Brief physical examination

The brief physical examination will include an assessment of the general appearance, abdomen, cardiovascular and respiratory system.

5.2.2 Vital signs

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

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

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

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

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

5.2.3 ECG

ECG will be performed in accordance with schedule provided in Table 1 and Table 2.

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

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

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 takes precedence and should be noted on the printout and recorded in the eCRF. ECG will be produced and quality checked and kept in case of further need for re-evaluation. It is highly recommended that the same machine is used for assessment throughout the patient's participation in the study.

ECG evaluation will be recorded in the eCRF.

5.2.4 Safety laboratory tests

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

Haematology and urinalysis will be assessed in line with the schedules provided in the Table 1 and Table 2.

Laboratory results should be reviewed by the Investigator/authorized delegate and evaluated for abnormalities. Any laboratory abnormalities considered to be significant in the investigators'/authorized delegate's judgement should be reported as described in Section 6.3.

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

Table 3 List of safety laboratory tests

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

[a] eosinophil, basophil and monocyte counts will be redacted from the central laboratory reports, except Visit 1 laboratory report (see Section 3.6).

5.2.4.1 Pregnancy Test

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

- Serum beta-HCG: To be done in all females at screening Visit 1 except for those who are NOT of child bearing potential as defined in inclusion criterion 3. This test is to be sent to and analysed at the 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 centre for all females at each clinical visit before IP administration except for those females who are NOT of child bearing potential as defined in inclusion criterion 3. A positive urine test result must be confirmed with serum beta HCG.

5.3 Other assessments and procedures

5.3.1 Weight and height

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

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

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

5.3.2 Patient reported outcomes

Patients will be supplied with an ePRO device and hand-held spirometer at Visit 2 after respiratory criteria have been confirmed (see Section 3.1, criterion 8 and 11). The study centre staff will be trained on how to use both devices and will be responsible for instructing patients on how to use both devices. Patients will have an opportunity to practice using the devices through a pre-programmed training module. Patients should be informed that the recordings made electronically cannot be retrospectively or prospectively entered and must be completed within a defined time window. Patients will also be provided with information about when and where to request help if problems occur.

5.3.2.1 Asthma daily diary

The Asthma Daily Diary will be completed each day from the evening of Visit 2 to the morning of Visit 17. The Asthma Daily Diary will include the following daily recordings: morning and evening home peak expiratory flow data (obtained from the home peak flow meter), asthma symptoms, inhalations of rescue medication, nights with awakenings due to asthma symptoms, background medication compliance. There will be triggers in the ePRO device to alert the patients to signs of worsening of asthma and to contact their physician in the setting of a diary alert, please refer to Section 5.1.1.

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

Home peak expiratory flow measurement

For details regarding peak expiratory flow measurement please refer to Section 5.1.3.

Asthma symptoms

Asthma symptoms during night time and daytime will be recorded by the patient each morning and evening in the Asthma Daily Diary, from Visit 2 to Visit 17.

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. Rescue medication usage is captured in the daily diary as the number of inhaler puffs and the number of times a nebulizer is used. Rescue medication usage will be summarized as the number of puffs with 1 instance of nebulizer use converted to 2 puffs.

Nocturnal awakenings

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

Background medication

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

5.3.2.2 Asthma control questionnaire (ACQ-6)

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

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

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤0.75

indicate well-controlled asthma, scores between 0.75 and <1.5 indicate partly controlled asthma, and a score ≥1.5 indicates not well controlled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered to be clinically meaningful.

The questionnaire will be completed using the ePRO device. An initial screening ACQ-6 will be taken at Visit 2 at the study centre. The patient will bring the device to the randomisation visit and complete the ACQ-6 on site during the randomisation visit (Week 0). Once randomised, patients will be asked to complete the ACQ-6 once every 4 weeks (±3day) until Week 8 and then once every 8 weeks (±3day) throughout the treatment period until Week 40. Patients will be asked to complete the ACQ-6 at EOT, Week 48 (+7day), or IPD visit.

Visit 2 ACQ-6 scores will determine eligibility for randomisation (see Section 3.1, inclusion criterion 15).

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 St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item PRO instrument developed to measure the health-related quality of life (HRQoL) of patients with airway diseases (Jones et al 1991). The questionnaire is divided into two parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and three domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall HRQoL. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible HRQoL and 0 indicates the best possible HRQoL. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment. Specific details on the scoring algorithms are provided by the developer in a user manual (Jones et al 2009).

The questionnaire will be completed using the ePRO device. The patient will bring the device to the study site. The patient should complete the questionnaire in a quiet area and be given as much time as needed to complete the assessment. Investigators should not clarify content and take care not to influence the patient's responses. The questionnaire will be checked by Investigator or designee for completeness, and be collected before the patient leaves the study site. At later visits, patients are not allowed to review their previous assessments.

The SGRQ will be completed by the patients prior to study drug administration at Visit 4 (Week 0, Day1), Visit 7 (Week 8), Visit 9 (Week 16), Visit 11 (Week 24), Visit 13 (Week 32), Visit 15 (Week 40) and Visit 17 (Week 48, or EOT) or IPD Visit.

5.3.3 Healthcare resource utilization

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

At Visit 1 Healthcare Resource Utilization (HRU) information will be collected with a 1 year recall period. In treatment period, HRU information will be collected with a recall period of 'since last visit'.

Note: Cases of hospitalization after Visit 1 also must be reported as an SAE (see Section 6.2 and 6.4).

5.3.4 Other run-in assessments

5.3.4.1 Serology

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

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

5.3.5 Pharmacokinetics

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

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

Serum will be collected according to the schedule of study procedures (see Table 2). On the dosing visits (Visit 4 and Visit 11), the serum will be collected as pre-dose.

Samples for determination of benralizumab concentration in serum will be analysed by a central laboratory on behalf of AstraZeneca, using a validated bioanalytical method. Following AZ standard process, bioanalytical lab will analyse PK samples only for patients receiving benralizumab based on the randomization/kit list.

After primary bioanalysis, residual PK sample aliquots may be retained for the purposes of re-analysis at AstraZeneca or designee for a maximum of 5 years after publication of the Clinical Study Report or as per local regulation, after which they will be destroyed. This is intended to allow AstraZeneca to investigate any anomalous results, or respond to regulatory authority questions. Samples will only be re-analysed according to the original purpose for which they were collected (eg PK analysis).

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

5.3.6 Immunogenicity

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

After primary bioanalysis, residual immunogenicity (ADA and nAb) sample aliquots may be retained for the purposes of re-analysis at AstraZeneca or designee for a maximum of 5 years after publication of the Clinical Study Report or as per local regulations, after which they will be destroyed. This is intended to allow AstraZeneca to investigate any anomalous results, or respond to regulatory authority questions. Samples will only be re-analysed according to the original purpose for which they were collected (eg ADA/nAb analysis).

Anti-benralizumab antibodies

Serum samples to measure presence of ADA will be collected according to the schedule of study procedures (see Table 2). On the dosing visits (Visit 4 and Visit 11), the serum will be collected as pre-dose.

The assessment of ADA will be determined in the serum samples using validated bioanalytical methods.

Neutralizing antibodies

All ADA positive samples will be tested for neutralizing antibodies (nAb). The presence or absence of neutralizing ADA will be determined using a validated bioanalytical method.

5.3.7 Handling of biological samples

5.3.7.1 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 B.

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.

5.3.7.2 Chain of custody of biological samples

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

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

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

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

5.3.8 Patient Testing Due to Public Health Crisis

If patient testing is performed due to the public health crisis, the results may be documented for this study.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

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

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

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

Adverse Events (AEs) for **malignant tumours** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

All AEs, including SAEs, will be collected from the time the patient signs the informed consent, and assent when applicable, throughout the treatment period and including the follow-up period (Visit 18, Week 56).

6.3.2 Follow-up of unresolved adverse events

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

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

6.3.3 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

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

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

6.3.4 Intensity rating scale

1 mild (awareness of sign or symptom, but easily tolerated)

2 moderate (discomfort sufficient to cause interference with normal activities)

3 severe (incapacitating, with inability to perform normal activities)

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 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.5 Causality collection

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

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

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

6.3.6 Adverse events based on signs and symptoms

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

6.3.7 Adverse events based on examinations and tests

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

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

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

6.3.8 Hy's Law

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

6.3.9 Symptoms of the disease under study

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

- The sign or symptom is serious according to definitions, see Section 6.2
- The patient discontinues the IP 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 randomisation, 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.

6.4 Reporting of serious adverse events

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

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

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

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

Once the investigators or other centre personnel indicate an AE is serious in the 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 centre personnel is to report the SAE to the appropriate AstraZeneca representative by telephone.

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

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

6.5 Overdose

- For this study, any dose of benralizumab greater than 200 mg will be considered an overdose.

- There is no specific treatment for an overdose with benralizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.
- An overdose with associated AEs will be recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms will be reported on the Overdose CRF module only.

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

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

For overdoses associated with the SAE, standard reporting timelines apply, see Section 6.4. For other overdoses, reporting should be done within 30 days.

6.6 Pregnancy

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

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, IP should be discontinued immediately. For pregnant patients, at IPD visit, pre-BD spirometry may be skipped, at the discretion of the Investigator.

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

If any pregnancy occurs in the course of the study, then investigators or other centre personnel 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 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the paper-based pregnancy outcome report is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

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 12 weeks after the last administration of IP. The investigators must obtain the consent of the subject's partner prior to obtaining information on the pregnancy.

6.7 Medication error

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix A.

6.8 Device Constituent Deficiencies

In a combination drug-device IMP (e.g. APFS), the Device Constituent deficiency is an inadequacy of a device constituent with respect to its identity, quality, durability, reliability, safety, or performance. These deficiencies include malfunctions, use errors, and information supplied by the manufacturer. Serious Adverse Device Effect (SADE) is defined as any Device Constituent Deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

- For device constituent deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.

- A remedial action is any action other than routine maintenance or servicing of a device constituent where such action is necessary to prevent recurrence of a device constituent deficiency. This includes any amendment to the device constituent design to prevent recurrence.

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the device constituent deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

6.8.1 SADE Reporting

NOTE: There are additional reporting obligations for device constituent deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to device constituents being used in clinical studies.

- Any device constituent deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device constituent deficiency.

- The sponsor will review all device constituent deficiencies and determine and document in writing whether they could have led to an SAE. These device constituent deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 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 4 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

7.2 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.

7.3 Storage

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

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

In the following cases:

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

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

7.4 IP administration and treatment Compliance

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

The IP will be administered at the study centre on treatment visits and within visit windows as specified in Table 2. In cases when a treatment visit cannot be scheduled within the specified window, the investigator should discuss with AZ Study Physician to decide whether the IP administration should be skipped.

If a patient misses more than 2 consecutive or non-consecutive doses of IP at any time within a calendar year, we strongly recommend a conversation between the investigator and the AZ study physician to review the patient's adherence to treatment and decide on the patient's disposition.

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

Before IP administration

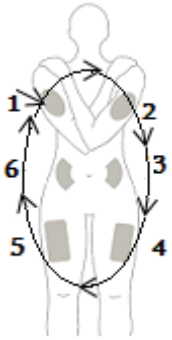
Prior to each IP administration:

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

IP administration

The IP will be administered by the Investigator/authorized delegate. It is advised that the site of injection of the IP be rotated such that the patient receives IP at a different anatomical site at each treatment visit. Suggested injection site rotation sequence is presented below (see Figure 3). The injection site must be recorded in the source documents and the eCRF at each treatment visit.

Figure 3 Injection sites and rotation scheme



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

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

After investigational product administration

After IP administration at the study site, the patient should be observed in case of any acute drug reactions in line with clinical practice .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 (e.g., viral illnesses)
- The patient is febrile (≥38°C; ≥100.4°F) within 72 hours prior to IP administration

7.5 Accountability

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

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

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

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

7.6 Concomitant and other treatments

7.6.1 Concomitant medication

Information about any treatment in the 6 months prior to the date of the informed consent, and assent when applicable, and all the concomitant treatments given during the study, with reason for the treatment, will be collected by the Investigator/authorized delegate at each visit (as shown in Table 1 and Table 2) and recorded in the eCRF.

7.6.1.1 Background medication

All patients are required to be treated with medium to high dose ICS-LABA for at least 6 months prior to Visit 1, documented medium to high dose ICS-LABA (≥500 mcg/day fluticasone propionate dry powder formulation or equivalent daily) for at least 3 months prior to Visit 1 and during the course of the study.

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

Background medication is not regarded as an IP, but will be provided by or reimbursed to 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 Section 3.1, criterion 6) will be provided by or reimbursed to AstraZeneca according to local regulations.

7.6.1.2 Rescue medication

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

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

7.6.2 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

7.7 Management of investigational product-related reactions

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

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

1 The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both, and at least 1 of the following: a) respiratory compromise; or b) reduced blood pressure or symptoms of end-organ dysfunction
2 Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms, and/or persistent gastrointestinal symptoms
3 Reduced blood pressure after exposure

Patients will have had a pre-assessment (i.e., vital signs and lung function) prior to IP administration and should be observed after IP administration at the study site for the appearance of any acute drug reactions.

In order to help understand the potential drug-relatedness of any acute reaction, a blood sample should be drawn as close as possible to the event for additional ADA testing (if not already scheduled for this visit). Serum tryptase or other blood testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the Investigator.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

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

8.2 Sample size estimate

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

The efficacy analyses will comprise both adults and adolescent patients.

For the primary endpoint annual asthma exacerbation rate, approximately 222 adults and adolescent patients with baseline blood eosinophil counts ≥300/μL per treatment arm (approximately 444 in total) will need to be randomised to achieve approximately 90% power CCI [redacted] As stated previously an about 2:1 ratio will be used for patients with baseline blood eosinophil counts ≥300/μL and <300/μL. Therefore the study will also randomise approximately 111 patients/arm (approximately 222 in total) with baseline blood eosinophil counts <300/μL. The <300/μL stratum will be closed for all patients, when a total of 222 adults and adolescent patients have been randomised in the stratum. So a total of approximately 666 adult and adolescent patients are expected to be randomised in the study. Among these 666 patients, at least 70% patients will be randomised from China.

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 analysed based on the safety analysis set.

8.3.1 All patients analysis set

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

8.3.2 Full analysis set

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

8.3.3 Safety analysis set

All patients who received at least 1 dose of IP will be included in the safety analysis set. Patients will be classified according to the treatment they actually received. A patient who has on 1 or several occasions received active treatment will be classified as active. All safety summaries and ADA data will be based on this analysis set.

8.3.4 Pharmacokinetic (PK) 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 and who had at least 1 measurable serum PK observation post first dose will be included in the PK analysis set. All PK summaries will be based on this analysis set.

8.4 Variables for analyses

8.4.1 Calculation or derivation of efficacy variables

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

8.4.1.1 Exacerbation rate

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

An asthma exacerbation is defined in Section 5.1.1.

In order to calculate the number of exacerbations experienced by a patient during the 48-week double-blind treatment period, the following rule will be applied.

The start of an exacerbation is defined as the start date of systemic corticosteroids, or the start date of a temporary increase in a stable oral corticosteroid background dose, or that start date of hospital admission, whichever occurs earlier. The end date is defined as the last day of systemic corticosteroids or the last day of a temporary increase in a stable oral corticosteroid background dose, or the date of discharge from a hospital, whichever occurs later. In the

primary analysis, the number of exacerbations observed for a patient during the 48-week double-blind treatment period will be used as response variable.

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

The primary analysis will include all available data including data collected after treatment discontinuation. Subjects will be encouraged to continue to undergo applicable study related visits/procedures for the full 48-week treatment period even after premature discontinuation of IP. Consequently, subjects lost to follow-up and subjects who withdraw their consent/assent will be the only source of missing information for the primary analysis. Maximum follow-up time for a patient during the treatment period is approximately 48 weeks; defined as the time from randomisation to the date of Visit 17. For a patient lost to follow-up or withdraw consent/assent, follow-up time will be defined as the time from randomisation to the time point after which an exacerbation could not be assessed.

In the statistical analysis, the number of asthma exacerbations experienced by a patient during the 48-week double-blind treatment period will be used as response variable, and the logarithm of the patient's corresponding follow-up time will be used as an offset in the analysis to adjust for patients having different exposure times during which the events occur.

For the production of summary statistics, the annual exacerbation rate per patient is calculated and standardized using data from the 48-week double blind treatment period according to the formula described below.

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

8.4.1.2 Proportion of patients with ≥1 asthma exacerbation during 48 weeks of treatment

The proportion of patients with ≥1 asthma exacerbation during the 48 weeks of treatment will be a supportive variable to the primary objective.

8.4.1.3 Time to first exacerbation

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

Start Date of first asthma exacerbation−Date of Randomisation+1.

The time to first asthma exacerbation for patients who do not experience an asthma exacerbation during the treatment period will be censored at the date of their last visit for the 48-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients or withdrawn patients).

8.4.1.4 Forced expiratory volume in 1 second

Pre-bronchodilator FEV_1 is a key secondary efficacy endpoint of this study, and the change from baseline to Week 48 is included in the testing strategy.

The change from baseline to each of the post-randomisation visits (post Visit 4) up to and including the end of 48-week double-blind treatment visit (Visit 17) will be used as secondary efficacy variables. The pre-bronchodilator measurement recorded at Visit 4 will be used as baseline FEV_1. If the Visit 4 pre-bronchodilator measurement is missing, the last non-missing pre-bronchodilator value before Visit 4 will be used as baseline instead.

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

The annual rate of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalization, as determined by the investigators will be a secondary efficacy variable.

The number of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalization experienced by a patient during the 48-week treatment period will be derived according to the following rule:

The number of asthma exacerbations experienced by a patient during the 48-week treatment period will be derived according to rule for the primary outcome variable in Section 8.4.1.1

In the statistical analysis, the number of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalization experienced by a patient during the 48-week double-blind treatment period will be used as response variable, and the logarithm of the patient's corresponding follow-up time will be used as an offset in the analysis to adjust for patients having different exposure times during which the events occur.

Maximum follow-up time for a patient during the 48-week double-blind treatment period is approximately 48 weeks, and the follow-up time is derived as described in Section 8.4.1.1.

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

8.4.2 Calculation or derivation of safety variable(s)

8.4.2.1 Safety variables

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

Change from baseline to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. The last non-missing measurement prior to the first dose of study treatment will serve as the baseline measurement for safety variables. AEs will be summarized by means of descriptive statistics and qualitative summaries.

8.4.3 Calculation or derivation of patient reported outcome variables

8.4.3.1 Asthma Symptom Score

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

Total asthma symptom score is a key secondary efficacy endpoint of this study, and the change from baseline to Week 48 is included in the multiple testing strategy.

8.4.3.2 Asthma Control Questionnaire (ACQ-6)

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

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

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

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

Furthermore, patients will be categorized according to their ACQ-6 end of treatment score as follows (Juniper et al 2006):

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

8.4.3.3 St. George's Respiratory Questionnaire (SGRQ)

The outcome variable for SGRQ will be change in total score from baseline to each of post-randomisation periods. Change in three domain scores from baseline to each of post-randomisation periods will be calculated separately.

A decrease of 4 units in the SGRQ total score compared to baseline has been established as the criterion for minimal meaningful improvement (Jones et al 2005). SGRQ responders will be those with a SGRQ total score $\geq$4 unit decrease.

8.4.3.4 Electronic diary variables

Asthma PROs (ACQ-6, SGRQ), 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 and each of the post-randomisation periods.

Biweekly (14 days) means will be calculated for daily assessments of asthma symptoms, night time awakenings, rescue medication usage and peak flow. Baseline will be the 14 days prior to randomisation and will be summarized as a mean. Post-randomisation biweekly (14 day) means will be calculated for each daily assessment and then summarized as group means for each 14-day period post-randomisation. ACQ-6 and SGRQ baseline will be the last observation prior to study drug administration and summarized as mean scores for each group. The change from baseline to each post-randomisation period will be used as secondary efficacy variable.

Rescue medication usage is captured in the daily diary as the number of inhaler puffs and the number of times a nebulizer is used. Rescue medication usage will be summarized as the number of puffs with 1 instance of nebulizer use converted to 2 puffs.

8.4.4 Calculation or derivation of pharmacokinetic variables

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

8.4.5 Calculation or derivation of immunogenicity variables

ADA result from each sample will be reported as either positive or negative. If the sample is positive, the ADA titer will be reported as well. In addition, the presence of neutralizing antibodies (nAb) will be tested in all ADA positive samples and the nAb results will be reported as positive or negative.

8.5 Methods for statistical analyses

The analysis of the primary and secondary endpoints will include all data captured during the 48-week treatment period regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence.

To control the type I error rate, a testing strategy will be applied to the primary (annual asthma exacerbation rate) and 2 key secondary endpoints (the change in FEV_1 and asthma symptom score from baseline to Week 48, respectively) for patients with baseline blood eosinophil counts ≥300/μL for benralizumab. The testing strategy will be according to the following gate keeping procedure:

Step 1: Perform the test of annual asthma exacerbation rate (benralizumab vs. placebo) at the family wise error rate (FWER) of 0.05. If the p-value is less than 0.05, then proceed to Step 2; otherwise no null hypothesis is rejected.

Step 2: Test the 2 key secondary endpoints at the FWER of 0.05 using a Holm Procedure (Holm 1979).

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

Additional analyses assessing the impact of Cases of Civil Crisis, Natural Disaster, or Public Health Crisis (e.g. SARS-CoV-2) may be included in the SAP.

8.5.1 Analysis of the primary variable (s)

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

The null hypothesis is that the exacerbation rate on benralizumab is equal to the exacerbation rate on placebo. The alternative hypothesis is that the exacerbation rate on benralizumab is not equal to the exacerbation rate on placebo, ie,

H_0: Rate ratio (benralizumab vs. Placebo) =1
H_a: Rate ratio (benralizumab vs. Placebo) ≠1

Exacerbation rate in the benralizumab group will be compared to exacerbation rate in the placebo group using a negative binomial model. The response variable in the model will be the number of asthma exacerbations over the 48-week treatment period. The model will include covariates of treatment group, region (China/non-China), number of exacerbations in the year before the study, and the use of maintenance oral corticosteroids (yes/no). The logarithm of the follow-up time will be used as an offset variable in the model.

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

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

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

8.5.2 Analysis of the secondary variable(s)

8.5.2.1 Analysis methods for secondary efficacy variables

Key secondary efficacy endpoints in this study are:

- Change from baseline in pre-bronchodilator FEV_1 at Week 48
- Change from baseline in asthma symptom total score at Week 48

Other secondary efficacy endpoints include

- Proportion of patients with ≥1 asthma exacerbation
- Time to the first asthma exacerbation

- Annual rate of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalization
- Change from baseline in total rescue medication use (average puffs/day)
- Change from baseline in morning and evening PEF at Week 48
- Change from baseline in asthma symptom day time/night time scores at Week 48
- Change from baseline in number of nights with awakening due to asthma and requiring rescue medication
- ACQ-6
- SGRQ

All the secondary efficacy endpoints will be analysed in patients with baseline blood eosinophil counts ≥ 300/μL. In addition, the 2 key secondary efficacy endpoints will be analysed in patients with baseline blood eosinophil counts < 150/μL, < 300/μL, 150-299/μL, 300-449/μL and ≥ 450/μL separately.

Change from baseline in pre-bronchodilator FEV1 at Week 48 will be compared between the benralizumab group and placebo using a repeated measures analysis on patients with a baseline pre-bronchodilator FEV1 and at least 1 post-randomisation pre-bronchodilator FEV1 in the full analysis set. The dependent variable will be the change from baseline in pre-bronchodilator FEV1 at post-baseline protocol-specified visits (up to the EOT Visit). Treatment group will be fitted as the explanatory variable, and region (China/non-China), baseline pre-bronchodilator FEV1, visit, the interaction term of visit and treatment, and the use of maintenance oral corticosteroids (yes/no) will be fitted as covariates. Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is:

*Change in FEV_1=Treatment group+baseline FEV_1+region+maintenance oral corticosteroids+visit+treatment*visit*

Change from baseline in asthma symptom total score; day time score, and night time score at Week 48 will be analysed separately using a similar model as the above model for change from baseline in pre-bronchodilator FEV_1.

The proportion of patients with ≥ 1 asthma exacerbation during the 48 weeks of treatment will be addressed as a supportive variable to the primary objective. The proportion in the benralizumab group will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for region (China/non-China), number of exacerbations in the year before the study, and the use of maintenance oral corticosteroids (yes/no).

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

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

Change from baseline in total rescue medication use (average puffs/days) and number of nights with awakening due to asthma and requiring rescue medication will be analysed using a similar model as for change from baseline in pre-BD FEV1.

Change from baseline in morning and evening PEF at Week 48 will be analysed separately using similar models as the model for change from baseline in pre-BD FEV1.

The ACQ-6 will be analysed in terms of change from baseline to end of treatment, change from baseline to each of post-randomisation periods, responder status at EOT (i.e. change from baseline to EOT $\leq$ -0.5), and asthma symptom control status at EOT (see Section 8.4.3.2 for categorization).

The SGRQ will be analysed in terms of change from baseline to end of treatment, change from baseline to each of post-randomisation periods in total score and three domain scores, and responders as defined by those with a SGRQ total score $\geq$4 unit decrease from baseline at EOT.

Change in mean score from baseline for ACQ-6 and change in total score from baseline for SGRQ (including the domain scores) will be analysed using a similar model as for change from baseline in pre-BD FEV1.

Responder variables for ACQ-6 (yes/no) and SGRQ (yes/no) will be analysed using a logistic regression model with covariates of treatment, region (China/non-China), baseline value, and the use of maintenance oral corticosteroids (yes/no).

8.5.2.2 Analysis methods for safety variables

AEs will be summarized by means of counts summaries by study period (treatment period and follow-up period). AEs will be listed for each patient and summarized by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by Medical Dictionary for Regulatory Activities (MedDRA). Laboratory safety variables will be summarized using standard

summary statistics and plots as appropriate. Other safety variables will be summarized as appropriate. Further details will be provided in the SAP.

Laboratory data for haematology and clinical chemistry will be summarized. The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Central laboratory reference ranges will be used for the identification of abnormalities, and a shift table will be produced for each laboratory parameter to display low, normal, high, and missing values. Shifts from normal to abnormal between baseline and post-baseline will be evaluated for urinalysis. Changes in vital signs will be examined at each visit and at endpoint. Baseline to maximum post-baseline and baseline to minimum post-baseline value shift tables will be generated, as applicable for each vital signs parameter. A shift table for ECG will be produced to display the Investigator assessment of normal, abnormal – not clinically significant, abnormal – clinically significant and not done between baseline and end of study. No separate summaries of physical examination findings will be produced since physical examination results will be presented in Medical History and AE summaries.

8.5.2.3 Analysis methods for pharmacokinetic variables

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

Benralizumab serum concentrations will be summarized using descriptive statistics by visit. Impact of ADA on PK will also be assessed.

The population PK analysis will be presented separately from the main clinical study report (CSR).

8.5.2.4 Analysis method for immunogenicity variables

Anti-drug antibodies (ADA) to benralizumab will be summarized using descriptive statistics by visit. ADA titers-time profiles of benralizumab by treatment group will be generated. The impact of ADA on PK and eosinophil level will be assessed. The potential association of ADA with safety and efficacy will be evaluated.

8.5.3 Subgroup analysis

To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analyses and statistical modeling including testing for interaction between treatment and covariates will be performed in patients with baseline blood eosinophil counts ≥300/μL for the following factors: Oral corticosteroids (OCS) use at baseline (yes, no), gender, age (<18, 18 - <65, and ≥65 years), region (China/non-China), country, BMI (≤35, >35 kg/m^2), the number of exacerbations during the previous year (2, ≥3 exacerbations), the number of exacerbations during medium-high ICS/LABA treatment prior to study enrolment (2, ≥3 exacerbations), ICS dose at study enrolment (medium, high) and nasal polyps (yes, no). Data will be analysed by negative binomial regression similar to the primary analysis and the same output will be presented for each subgroup as for the primary analysis. For the

statistical modeling including interaction effects, the estimate of the interaction effects will be presented together with the corresponding p-value. These analyses are to be considered as exploratory and will be performed on the full analysis set.

8.5.4 Sensitivity analysis

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

8.5.5 Interim analysis

There is no interim analysis planned for this study. The study will remain blinded until database lock.

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 the diagnosis of: 1) Investigator-reported non-fatal myocardial infarction, unstable angina, non-fatal stroke (hemorrhagic, ischemic, embolic), as well as all deaths and 2) Investigator-reported malignancies during the study. The committee will operate in accordance with an Adjudication Committee Charter/Manual of Operations, which will also provide detail on specific information to enable a more robust review through adjudication process.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

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

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

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

9.2 Monitoring of the study

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

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

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

9.2.1 Source data

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

9.2.2 Recording of data

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

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

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

9.2.3 Study agreements

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

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

9.2.4 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

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

AstraZeneca reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

meet individual stopping criteria or are otherwise considered significant

are assessed as causally related to study drug,

are not considered to be consistent with continuation of the study

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

In terminating the study, AstraZeneca will ensure that adequate consideration is given to the protection of the subjects’ interests

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or Good Clinical Practice (GCP) guidelines
Inadequate recruitment of participants by the investigator
Discontinuation of further study intervention development

9.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Centre staff or other party, according to the Data Management Plan.

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

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 WHO Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre or other party.

The Web Based Data Capture (WBDC) system will be used for data collection and query handling. Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail. The Investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

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

The Investigator will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked. A copy of the completed electronic Case Report Forms will be archived at the study centre.

Serious Adverse Event (SAE) Reconciliation

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

Data associated with human biological samples

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

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

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

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

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

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

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

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

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

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent/Assent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

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

Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

10.4 Informed consent/assent

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

- Ensure each patient, parent or legal guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study (before any study procedures are performed) as per local requirements. The Informed Consent/Assent Form needs to be adjusted as per local requirements.
- Ensure each patient, parent or legal guardian is notified that they are free to discontinue from the study at any time.
- Ensure that each patient, parent or legal guardian is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient, parent or legal guardian provides signed and dated Informed Consent/Assent Form before conducting any procedure specifically for the study. Local regulations are to be followed in determining the assent/consent requirements for children of different age groups.
- Ensure the original, signed Informed Consent/Assent Form(s) is/are stored in the Investigator's Study File and kept for a period that is complaint with GCP/local regulatory requirements, whichever is longer.
- Ensure a copy of the signed Informed Consent/Assent Form is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the Informed Consent/Assent Form that is approved by an Ethics Committee EC/IRB.

10.5 Changes to the protocol and informed consent form/assent form

Study procedures will not be changed without the mutual agreement of the international co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a change to a Clinical Study Protocol requires a change to a study centre's Informed Consent Form, AstraZeneca and the study centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

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

10.6 Audits and inspections

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

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12. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Additional Safety Information

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

Life threatening

'Life-threatening' means that the patient 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 patient'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 patient 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 patient or may require medical intervention to prevent 1 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 (e.g., 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

When making an assessment of causality, consider the following factors 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 patient 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?
- De-challenge 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.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

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?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.
occurred
was identified and intercepted before the participant received the drug
did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:
Drug name confusion
Dispensing error e.g., medication prepared incorrectly, even if it was not actually given to the participant
Drug not administered as indicated, for example, wrong route or wrong site of administration
Drug not taken as indicated e.g., tablet dissolved in water when it should be taken as a solid tablet
Drug not stored as instructed e.g., kept in the fridge when it should be at room temperature
Wrong participant received the medication (excluding IVRS/IWRS errors)
Wrong drug administered to participant (excluding IVRS/IWRS errors)

Examples of events that do not require reporting as medication errors in clinical studies:
Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
Participant accidentally missed drug dose(s) e.g., forgot to take medication
Accidental overdose (will be captured as an overdose)
Participant failed to return unused medication or empty packaging
Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix B 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. 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 e.g., 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 e.g., 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
- 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.

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

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 (FDA 2009).

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.

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, e.g., 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.

Identification of potential hy's law cases

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

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

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

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

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

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

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

Follow-up

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.

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

Review and Assessment of potential hy's law cases

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

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

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[2] 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 Potential Hy's Law criteria met of this Appendix.

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 Actions required when potential Hy's law criteria are met before and after starting study treatment?

If No: follow the process described in Potential Hy's Law criteria met of this Appendix

[2] 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.

If Yes:

Determine if there has been a significant change in the patient's condition[#3] 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 Potential Hy's Law criteria met of this Appendix

[3] 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.

Appendix D Anaphylaxis: definition, signs, symptoms and management

Introduction

As with any antibody, allergic reactions to dose administration are possible. The World Health Organization (WHO) has categorized anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic [IgE-mediated and non-IgE-mediated (e.g., IgG and immune complex mediated) and nonimmunologic (Kemp et al 2008). The clinical criteria for defining anaphylaxis for this study are listed in Clinical Criteria for Defining Anaphylaxis and Immune Complex Disease. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Signs and Symptoms and Management of Acute Anaphylaxis.

Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc, and medical equipment to treat anaphylactic reactions should be available at study sites, and study personnel should be trained to recognise and treat anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs, a blood sample should be drawn from the patient as soon as possible after the event, at 90 minutes±30 minutes after the event, and at discharge for analysis of serum tryptase at a local laboratory. Other blood testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the Investigator.

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 (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

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

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

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

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

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

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

(d) Persistent gastrointestinal symptoms (e.g., 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.

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

Management of Acute Anaphylaxis

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.

Possibly appropriate, subsequent measures depending on response to epinephrine

1. Place patient in recumbent position and elevate lower extremities.

2. Establish and maintain airway.

3. Administer oxygen.

4. Establish venous access.

5. Normal saline IV for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate

1. Consider epinephrine infusion.

2. Consider H1 and H2 antihistamines.

3. Consider nebulized β2 agonist [e.g., albuterol (salbutamol)] for bronchospasm resistant to epinephrine.

4. Consider systemic corticosteroids.

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

6. Consider glucagon for patient taking b-blocker.

7. Consider atropine for symptomatic bradycardia.

8. Consider transportation to an emergency department or an intensive care facility.

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

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 (CFC)	>500 - 1000	>1000 - 2000
Beclomethasone dipropionate (HFA)	>240 - 480	>480
Beclomethasone dipropionate (Fostair)	>200 - 400	>400 - 800
Budesonide	>400 to 800	>800 - 1600
Budesonide, if as delivered dose (e.g. Symbicort)	>320 to <640	≥640 - 1280
Ciclesonide	>160 - 320	>320 - 1280
Flunisolide	>1000 - 2000	>2000
Fluticasone propionate (DPI)	>250 - 500	>500 - 1000
Fluticasone propionate (HFA)	>250 - 500	>500
Fluticasone furoate (DPI)	NA	200
Mometasone furoate	>220-440	>440
Triamcinolone acetonide	>1000 - 2000	>2000

Note: Categories of "medium" and "high" doses are based on published information and available studies (at the time of GINA 2018 publication), including direct comparisons where available. Doses may be country-specific depending on labelling requirements. For new preparations, manufacturer's information should be reviewed carefully; products containing the same molecule may not be clinical equivalent (GINA 2018).

Appendix F Restricted and prohibited medications

Asthma medication restrictions

Table 5 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 visit 1 and throughout the study (unless there is a medical need as judged by the Investigator and discussed beforehand with AstraZeneca Study Physician) Usual ICS-LABA should not be taken prior to scheduled spirometry, ECG and home PEF assessments (to be administered once assessments are completed)
Short acting beta2-agonists (SABA)	Restricted	Regular scheduled use in the absence of any asthma symptoms and/or planned exercise is discouraged from Visit 1 throughout the study. Rescue use of SABA administered via nebulisation is allowed. SABA should not be used within 6 hours prior to scheduled spirometry, ECG and home lung function assessments.
Additional Maintenance Controllers (e.g. LTRAs, tiotropium, cromone, theophylline and oral corticosteroids)	Restricted	Have been used for at least 1 month prior to Visit 1; stable dose during the treatment period. Usual controller should not be taken prior to scheduled spirometry, ECG and home PEF assessments (to be administered once assessments are completed).
Short acting anticholinergics (e.g. ipratropium)	Restricted	Not allowed from Visit 1 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 Visit 1 and throughout the study duration

Maintenance and Reliever Treatment)		
Five- lipoxygenase inhibitors (e.g. Zileuton)	Prohibited	Not allowed 30 days prior to Visit 1; during treatment period

Other medication restrictions. Usage of the following restricted medications might be acceptable for AE treatment after discussion with AstraZeneca Study Physician.

Table 6 Other medication restrictions

Medication	**Prohibited/restricted**	**Details**
Live Attenuated Vaccines	Prohibited	Not allowed 30 days prior to randomisation; during treatment period, and 12 weeks after the Last Dose of the investigational product
Inactive/killed vaccinations (e.g. inactive influenza)	Restricted	Allowed provided they are not administered within 1 week before/after any IP administration.
Any immunomodulators or Immunosuppressives	Prohibited	Not allowed within 3 months or 5 Half Lives (whichever is longer) prior to the date informed consent is obtained; during treatment period; 3 Months after Last Dose
Any immunomodulators or immunosuppressives – topical	Restricted	Topical administration of immunosuppressive medication may be allowed at the discretion of the Investigator after discussion with the AstraZeneca Study Physician
Blood products or immunoglobulin therapy	Prohibited	Not allowed 30 days prior to date of ICF; during treatment period.
Any marketed (e.g. omalizumab) or investigational biologic treatment	Prohibited	Not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1; during treatment period; 12 weeks 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 randomisation; during treatment period; and 12 weeks after the last dose of the investigational product
Allergen Immunotherapy	Restricted	Allowed if on stable therapy, or stable seasonal therapy, for at least 30 days prior to date of ICF; Immunotherapy injections must be separated from IP injections by at least 7 calendar days
Herbal remedies with bronchiectasic effect	Prohibited	Not allowed 30 days prior to Visit 1; and through out study period
Roflumilast	Prohibited	Not allowed 30 days prior to Visit 1; during treatment period
Non-selective oral or ophthalmic β-adrenergic antagonist (e.g. propranolol)	Prohibited	Patients currently using any non-selective oral or ophthalmic β-adrenergic antagonist at the time of Visit 1 are not eligible for the study. Not allowed during treatment period.
Medications not currently licensed for use in the treatment of asthma and not part of current standard of care	Prohibited	Not allowed within 30 days prior to randomisation; throughout the duration of the study

Appendix G Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation .

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the patient's safety. If in doubt, please contact the AZ Study Physician.

G 1 Reconsent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections G 2 to G 6. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

G 2 Rescreening of Patients To Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a patient and either enrolment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in Section 4 Table 1, the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a patient in addition to that detailed in Section 4.1.3. The procedures detailed in Section 3.1 and 3.2 must be undertaken to confirm

eligibility using the same randomization number as for the patient.

G 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service may visit the patients home / or other remote location as per local Standard Operating Procedure (SOPs), as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the clinical study protocol (CSP).

G 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow adverse events, concomitant medication, and other information including efficacy data where relevant to be collected according to study requirements to be reported and documented.

G 5 At-home or Remote Location IP Administration Instructions

If a site visit is not possible, at-home or remote location administration of IP may be performed by a qualified HCP, provided this is acceptable within local regulation/guidance, or by the patient or his/her caregiver. The option of at-home or remote location IP administration ensures patients safety in cases of a pandemic where patients may be at increased risk by traveling to the site/clinic. This will also minimize interruption of IP administration during other study disruptions, eg, site closures due to natural disaster.

G 5.1 At-home or Remote Location IP Administration by a Qualified HCP or TPV Service

A qualified HCP from the study site or TPV service may administer the IP at the patient's home or other remote location according to the CSP. All necessary supplies and instructions for administration and documentation of IP administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit.

G 5.2 At-home or Remote Location IP Administration by the Patient or His/Her Caregiver

Prior to at-home or remote location IP administration the investigator must assess the patient or his/her caregiver to determine whether they are appropriate for at-home or

remote location administration of IP. Once the patient or his/her caregiver is deemed appropriate for at-home or remote location administration, he/she must receive appropriate training. All necessary supplies and instructions for administration and documentation of IP administration will be provided. More information related to the visit can be obtained via a telemedicine or home / remote visit.

G 6 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home / remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the patient themselves.

Appendix H Protocol Amendment History

Version 4.0, 17th Dec 2019

Changes to the protocol are summarised below:

The main purpose of the Version 4 protocol changes is to augment the eligibility criteria to enrol a population more aligned to the global Phase 3 program patient population. Further updates provide operational clarifications and correct grammatical errors in the previous versions of the protocol.

- In Protocol Synopsis, replacing "This study will be conducted regionally in approximately 70 study centres in China and other countries. Target is to randomise approximately 666 patients, among which approximately 534 will be randomised from China" with "This study will be conducted regionally in approximately 90 study centres in China and other countries. Target is to randomise approximately 666 patients, among which approximately 80% will be randomised from China". This clarification is made to allow operational flexibility in patient management and randomisation across eosinophil strata and to reflect the potential change of number of study centres and the number of patients from China.
- In Protocol Synopsis, updating the estimated date of last patient completed from "Q3 2020" to "Q3 2022" to reflect the potential change of recruitment timeline based on current study recruitment date.
- In Protocol Synopsis, section 1.2, section 1.4, replacing "Patients will be stratified by country/region, age group (adult or adolescent), and peripheral blood eosinophil count at time of Visit 1 (<300 or ≥300 cells/μL)." by "Patients will be stratified by country/region (the mainland of China, Taiwan, South Korea or Philippine), age group (adult or adolescent), and peripheral blood eosinophil count at time of Visit 1 (<300 or ≥300 cells/ μL)." to clarify the countries/regions randomising patients.
- In Protocol Synopsis, section 1.4, Section 3.10.2, replacing "1. The eosinophil <300/μL stratum will be closed to all the patients from China when the total number of Chinese patients in the stratum reaches approximately 178." with "1. The eosinophil <300/μL stratum will be closed to all the patients from China when the total number of Chinese patients in the stratum reaches approximately 166", as non-China countries reached their target allocation in the low eosinophil strata by the time protocol amendment 3 was approved by the local EC. The strata number was adjusted to maintain the total overall sample size of 666 patients.
- In Protocol Synopsis, Section 2.1, Section 5.1.1 replacing "An emergency room/urgent care visit (defined as evaluation and treatment for < 24 hours in an Emergency department (ED) or urgent care centre) due to asthma that required systemic corticosteroids for (as per above)" with "An emergency room/urgent care visit (defined as evaluation and treatment for < 24 hours in an Emergency department

(ED) or urgent care centre) due to asthma that required systemic corticosteroids for at least 3 days (as per above)" to clarify the exacerbation definition.

- In Protocol Synopsis, Section 2.2, replacing "to evaluate the pharmacokinetics and immunogenicity of benralizumab" by "to characterize the PK and immunogenicity of benralizumab", "PK parameters" by "PK: Serum trough concentrations" and "Anti-drug antibodies (ADA)" by "ADA: Incidence of anti-drug antibodies" to clarify only concentration data will be analysed and the PK parameters will not be calculated.
- In Protocol Synopsis, the covariate "country" included in the statistical models for primary and secondary endpoints is replaced by "region (China/non-China)" due to the limited number of patients in non-China countries.
- In Protocol Synopsis, deleting the duplicate sentence "The primary endpoint and the 2 key secondary endpoints will be analysed using the patients with baseline blood eosinophils ≥300/ μL according to a gate-keeping procedure."
- In Protocol Synopsis and section 1.4, section 8.2, replacing "Approximately 666 patients are expected to be randomised in the study with approximately 534 patients (267 patients/arm) to be enrolled from China." by "Approximately 666 patients are expected to be randomised in the study with approximately 80% patients to be randomised from China.", to clarify that the sample size represents the number of randomised patients and to allow operational flexibility to manage patient randomisation in China and non-China countries.
- In Protocol Synopsis, replacing "The efficacy analyses will comprise both adult and adolescent patients." by "The efficacy and safety analyses will comprise both adult and adolescent patients." to clarify the safety analyses of the adolescent is also consistent with adults.
- In Section 3.1, Inclusion 3, replacing "includes" by "include", replacing "postementopausal" to "postmenopausa" to correct the spelling error. Inclusion criterion 6, adding "Documented treatment with medium to high dose ICS and a LABA for at least 3 months prior to Visit 1 with or without oral corticosteroids and additional asthma controllers. The ICS and LABA can be part of a combination product or given by separate inhalers. Equivalents for fluticasone propionate dry powder can be found in Appendix E, Background Therapy Equivalence Table.

  The ICS dose must be ≥500 mcg/day fluticasone propionate dry powder formulation or equivalent daily. For ICS/LABA combination preparations, the highest approved maintenance dose in the local country will meet this ICS criterion.

  If patients use more than one type of ICS-containing therapy, each should be converted to fluticasone propionate equivalents and summed to derive the patient's total daily dose." to optimize the eligibility criteria.

- In section 3.1, Inclusion criterion 8, replacing "At least 2 documented asthma exacerbations in the 12 months prior to the date informed consent, and assent, at least 1 of 2 exacerbations should occur during the treatment of medium-to-high dose ICS-LABA, when applicable is obtained that required use of a systemic corticosteroid or a temporary increase from the patient's usual maintenance dose of oral corticosteroid (please refer to Section 4.1.1). For patients who are re-screened within 30 days of their screen failure date, the calculation of the 12 month period should be done from the original informed consent, and assent when applicable date." by "At least 2 documented asthma exacerbations in the 12 months prior to the date of informed consent, and assent when applicable, during the treatment of medium-to-high dose ICS-LABA, that required use of a systemic corticosteroid or a temporary increase from the patient's usual maintenance dose of oral corticosteroid (please refer to Section 4.1.1). For patients who are re-screened within 30 days of their screen failure date, the calculation of the 12-month period should be done from the original informed consent, and assent date" to correct the grammar.
- In Section 3.1, adding Inclusion criterion 15 "Pre-bronchodilator (Pre-BD) FEV1 of <80% predicted (<90% predicted for patients aged 12 to 17 years) at Visit 2" to more closely align the eligibility criteria with the global Phase 3 program patient population.
- In Section 3.1, adding Inclusion criterion 16 "ACQ-6 score ≥1.5 at Visit 2" to more closely align the eligibility criteria with the global Phase 3 program patient population.
- In Section 3.1, removing "inclusion criteria at randomisation", adding footnote "*" No.1 to No.9, No.15 and No.16 are the inclusion criteria at screening; No. 10 to No. 14 are the inclusion criteria at randomisation. to differentiate and clarify the inclusion criteria at screening and randomisation.
- In Section 3.2, exclusion criterion 1, replacing "Clinically important pulmonary disease" by "Known history of clinically important pulmonary disease" to establish the presence of previous history.
- In Section 3.2, exclusion criterion 2, replacing "Any disorder" by "Known history of any disorder" to establish the presence of previous history.
- In Section 3.2, exclusion criterion 4, replacing "History of anaphylaxis to any biologic therapy" by "Known history of anaphylaxis to any biologic therapy" to establish the presence of previous history.
- In Section 3.2, exclusion criterion 8, replacing "Any clinically significant cardiac disease" by "Known history of any clinically significant cardiac disease" to establish the presence of previous history.
- In Section 3.2, exclusion criterion 10, replacing "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." by "Current active liver disease: Chronic stable hepatitis B and C (including positive testing for hepatitis B surface antigen (HBsAg) or hepatitis C

antibody), or other stable chronic liver disease are acceptable if subject otherwise meets eligibility criteria. Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.

Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥3 times the upper limit of normal (ULN), confirmed by *repeated testing during screening period (AST or ALT>5xULN if documented HES with liver manifestations). Transient increase of AST/ALT level that resolves by the time of randomisation is acceptable if in the Investigator's opinion the subject does not have an active liver disease and meets other eligibility criteria.

Note: The patients previously screen failed in this study due to this criterion are allowed to be rescreened if they meet this updated criterion. " to keep consistency with the latest benralizumab project specific safety requirement.

- In Section 3.2, exclusion criterion 11, replacing "Immunodeficiency disorder" by "Known history of immunodeficiency disorder" to establish the presence of previous history.
- In Section 3.2, exclusion criterion 13, replacing "Cancer" by "Known history of cancer" to establish the presence of previous history.
- In Section 3.2, Section 3.4, removing "enrolled" as an incorrectly enrolled patients is categorised as a are screen failures and is not applicable in section of incorrectly randomised.
- In Section 3.3, replacing "The randomisation will be stratified by country/region, age group (adult or adolescent), and blood eosinophil count at Visit 1 (≥300/μL or <300/μL) and the randomisation numbers will be grouped in blocks." by "The randomisation will be stratified by country/region (the mainland of China, Taiwan, South Korea or Philippine), age group (adult or adolescent), and blood eosinophil count at Visit 1 (≥300/μL or <300/ μL) and the randomisation numbers will be grouped in blocks.", to clarify the country/regions randomising patients.
- In Section 3.3, replacing "Randomised patients, who discontinue from the IP administration, will not be replaced." by "Withdrawn patients, who discontinue from IP or withdraw from study, will not be replaced. If a patient withdraws from the study, then his/her enrolment number/randomisation code cannot be reused.", to provide clarity to replacement of withdrawn patients.
- In Section 3.4, replacing "Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients, who are enrolled but subsequently found not to meet all the eligibility criteria, must not be randomised or initiated on treatment, and must be withdrawn from the study." by "Patients who fail to meet the eligibility criteria should not, under any circumstances, be randomised or receive study medication. There can be no exceptions to this rule. Patients, who are enrolled but are subsequently found not to meet all the eligibility criteria, must not be randomised or

initiated on treatment, and must be screen failed from the study." for operational clarity.

- In Section 3.4, adding "Study treatment must be discontinued in cases where continued treatment is deemed to pose a safety risk to the subject. In those cases where continuation of the study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented. Regardless of what is decided about continuation of IP or not, all randomised subjects should be encouraged to remain in the study and continue to be followed up in accordance with defined study procedures." to provide clarity to patient management for incorrectly randomised patients.
- In Section 3.5, adding "The randomisation code will be assigned from a randomisation list prepared by a computerized system provided by Parexel Informatics on behalf of AZ (AZRand)." to provide more details regarding the generation of randomisation list.
- In Section 3.5, replacing "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." by "Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomised or receive study medication. There can be no exceptions to this rule.", to clarify that this statement applies to randomised patients and not to an enrolled patient. Enrolled patients that do not meet the inclusion/exclusion criteria will not be randomised.
- In Section 3.6, replacing "The study will be conducted in double-blind fashion." by "The study is a double-blind study", to correct a grammatical error.
- In Section 3.6, adding "site staff" in the sentence "AstraZeneca staff involved in the study, the patients, and the investigators/site staff involved in the treatment of the patients or in their clinical evaluation will not be aware of the treatment allocation." to clarify that not only investigators but all sites staff will not be aware of the treatment allocation.
- In Section 3.6, adding "Regarding lab results obtained during the treatment period but ordered outside of the clinical trial, centre staff who are directly involved in the patient's treatment and evaluation should remain blinded to any eosinophil, basophil and monocyte results included as part of outside lab reports.", to provide clarity to blinding procedures for laboratory results obtained from any laboratory.
- In Section 3.7, replacing "Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator(s) or pharmacists at the study centre from the IWRS/IVRS." by "Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator(s) or delegate at the study centre from the IWRS/IVRS.", to clarify that only the Investigator or delegate can perform emergency unblinding.
- In Section 3.8.1 (d), deleting "Please refer to Section 3.1, inclusion criterion 7 for examples of allowed additional controller therapies for this study." as duplicate sentence in the section.

- In Section 3.8.1 (d), replacing "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 physician. All changes in the patient's background medication should be documented in source along with rationale for change and recorded in eCRF." by "Changes to the patient's background controller regimen are discouraged during the treatment period, unless judged medically necessary by the Investigator. All changes in the patient's background medication should be discussed beforehand with the AstraZeneca study physician and documented in source along with rationale for change and recorded in eCRF.", to clarify the rationale for changing a patient's background medication should be discussed with the AZ physician.

- In Section 3.8.1, (e) Asthma medication restrictions on the days of scheduled spirometry visit, replacing "Screening Visit 2: Patients should withhold their usual ICS, LABA, or LAMA medications on the morning of the FEV1 measurement and reversibility test. Twice daily ICS- LABA therapies should be withheld for 12- 24 hours; once daily therapies containing ICS, LABA, or LAMA therapies should be withheld for ≥24 hours for eligibility assessment (see Section 3.1, inclusion criterion 9)." by "Screening Visit 2: Patients should withhold their usual ICS, LABA, LAMA, LTRA or theophylline medications on the morning of the FEV1 measurement and reversibility test. Twice daily ICS- LABA therapies should be withheld for 12- 24 hours; once daily therapies containing ICS, LABA, LAMA, LTRA, theophylline therapies should be withheld for ≥24 hours for eligibility assessment (see Section 3.1, inclusion criterion 8).", to include relevant medications (LTRA, theophylline) based on the ATS (American Thoracic Society) guideline.

- In Section 3.8.1, (e) Asthma medication restrictions on the days of scheduled spirometry visit, replacing "Treatment Visits 4-17: Patients should withhold their usual ICS, LABA, or LAMA medications on the morning of the scheduled spirometry. Twice daily ICS-LABA therapies should be withheld for 12- 24 hours; once daily therapies containing ICS, LABA, or LAMA therapies should be withheld for ≥24 hours prior to the spirometry assessment. This is especially important prior to scheduled spirometry assessments (see Table 2) in order to maintain the integrity of planned efficacy analyses around lung function improvement. In addition, SABA should not be used within 6 hours prior to the spirometry assessments. The patient's usual asthma controller medications may be administered following completion of the pre-BD spirograms. The suggested order of administration of the patient's usual asthma controller and IP administration relative to scheduled pre -BD spirometry is given in Section 5.1.2.
  If the patient has taken their usual ICS, LABA, or LAMA asthma controller medication on the morning of the scheduled spirometry visit, the Investigator/authorized delegate should remind the patient of the importance of withholding their usual morning asthma medication, and reschedule the visit for another day, within the allowed window." by "Treatment Visits 4-17: Patients should withhold their usual ICS, LABA, LAMA, LTRA or theophylline medications on the morning of the scheduled spirometry. Twice daily ICS-LABA therapies should be withheld for 12- 24 hours; once daily therapies containing ICS, LABA, LAMA, LTRA or theophylline therapies should be withheld for ≥24 hours prior to the

spirometry assessment. This is especially important prior to scheduled spirometry assessments (see Table 2) in order to maintain the integrity of planned efficacy analyses around lung function improvement. In addition, SABA should not be used within 6 hours prior to the spirometry assessments. The patient's usual asthma controller medications may be administered following completion of the pre-BD spirograms. The suggested order of administration of the patient's usual asthma controller and IP administration relative to scheduled pre -BD spirometry is given in Section 5.1.2.
If the patient has taken their usual ICS, LABA, LAMA, LTRA or theophylline 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." to include relevant medications (LTRA, theophylline) based on the ATS (American Thoracic Society) guideline.

- In Section 3.8.2, Section 3.8.3, Section 6.6.2, removing "(5 half-lives)" due to 16 weeks is longer that 5 benralizumab being longer than half-lives, which is more conservative.
- In Section 3.9.1, replacing "Adverse events will be followed up (See Section 6);" by "For patients who are not willing to continue to participation in the study, adverse events will be followed up outside of the clinical study (See Section 6);" to clarify the requirement of continuous follow-up the adverse events, which can be done outside of the clinical study for patients withdrawal from the study.
- In Section 3.9.1, replacing "All patients who prematurely discontinue IP should return to the study centre and complete the procedures described for the Premature IP Discontinuation visit (IPD) within 4 weeks (+7 days) after the last dose of IP. At that visit, patients should be encouraged to remain in the study to complete all subsequent study visits, procedures and assessments or alternatively agree to be contacted by phone calls at monthly intervals in order to collect AEs/SAEs, changes in concomitant medication, health care utilisation, and asthma exacerbation information. Patients not willing to continue to participate in the study should return to the study centre 1 last time at 12 weeks (±7 days) after the last dose of IP for final study related assessments." by "All patients who prematurely discontinue IP should return to the study centre and complete the procedures described for the Premature IP Discontinuation visit (IPD) within 4 weeks (+7 days, for the last dose being either the first or the second dose) or 8 weeks (+7 days , for the last dose being the third or the following dose) after the last dose of IP. At that visit, patients should be encouraged to remain in the study to complete all subsequent study visits, procedures and assessments or alternatively agree to be contacted by phone calls at monthly intervals in order to collect AEs/SAEs, changes in concomitant medication, health care utilisation, and asthma exacerbation information. Patients not willing to continue to participate in the study should return to the study centre 1 last time at 12 weeks (±7 days, for the last dose being either the first or the second dose) or 16 weeks (±7 days, for the last dose being the third or the following dose) after the last dose of IP for final study related assessments.", to clarify the various scenarios and procedures when a patient discontinues IP.

- In Section 3.10, replacing "Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded in eCRF as 'Screen failure' (the potential patient who does not meet one or more criteria required for participation in a trial, this reason for study withdrawal is only valid for not randomised patients). 'Failure to meet randomisation criteria' should be selected for an indication that the patient has been unable to fulfil/satisfy the criteria required for assignment into a randomised group (it is only applicable for randomised studies and should be used for patient withdrawal post-screening)." by "Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded in eCRF as 'Screen failure' (the potential patient who does not meet one or more criteria required for participation in a trial, this reason for study withdrawal is only valid for not randomised patients). No further study related follow-up of these patients is required. 'Failure to meet randomisation criteria' should be selected for an indication that the patient has been unable to fulfil/satisfy the criteria required for assignment into a randomised group (it is only applicable for patient found not meeting criteria after randomisation).", to clarify there is no follow-up action for patients that are screened failed and the definition of "Failure to meet randomisation criteria" in eCRF.
- In Section 3.10.2, replacing "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." by "The reason of withdrawal should be documented in the source and eCRF as a development of study specific withdrawal criteria. As with screen failures, no further study related follow-up of these patients is required.", to clarify this is applicable for patient withdrawal and keep consistency with other sections/study documents.
- In Section 3.10.3, replacing "If patient agrees, he/she will be asked to return to the study centre and complete procedures described for the IPD (Premature IP Discontinuation) visit and for patients who are not willing to continue to participate in the study, he/she will complete IPD and Follow-up visit within 4 weeks (+7 days) and 12 weeks (±7 days) after the last dose of IP, respectively." by "If patient agrees, he/she will be asked to return to the study centre and complete procedures described for the IPD (Premature IP Discontinuation) visit. For patients who are not willing to continue to participate in the study, he/she will complete IPD within 4 weeks (+7 days, for the last dose being either the first or the second dose) or 8 weeks (+7 days, for the last dose being the third or the following dose) after the last dose of IP and Follow-up visit 12 weeks (±7 days for the last dose being either the first or the second dose) or 16 weeks (±7 days, for the last dose being the third or the following dose) after the last dose of IP, respectively.", to clarify the IPD visit timeframe and various scenarios for patients that prematurely discontinue IP.
- In Section 3.10.5, new section added: adding the whole section,
"3.10.5 Withdrawal due to repeat exacerbations during screening
Patients who experience more than 1 asthma exacerbation between Visit 1 and Visit 4 will not be randomised and will be withdrawn from the study (see Section 4.1.3.1).

The start of an exacerbation is defined as the start date of systemic corticosteroids, or the start date of a temporary increase in a stable oral corticosteroid background dose, or that start date of hospital admission, whichever occurs earlier. The end date is defined as the last day of systemic corticosteroids or the last day of a temporary increase in a stable oral corticosteroid background dose, or the date of discharge from a hospital, whichever occurs later (see Section 8.4.1.1).
Patients who are diagnosed with an asthma exacerbation at Visit 4 will not be randomised and will be withdrawn from the study (see Section 4.1.3.1).
The reason for withdrawal should be documented in the source and eCRF as a development of study specific withdrawal criteria. Patients who are withdrawn due to exacerbation at Visit 4 or due to exacerbations between Visit 1 and Visit 4 may be re-screened twice (see Section 4.1.3.1). ",
to clarify the special withdrawal case that subject should be withdrawn/screened failed if more than 1 exacerbation occurs during the screening period, which has not been specified in Section 3.10.1.

- In Section 4, Table 1, adding "ACQ-6" assessment added to visit 2 to align with the updated eligibility criteria.
- In Section 4, Table 2, replacing note [#] "Unscheduled visits may be initiated as needed, and additional assessments performed at these visits, at the discretion of the Investigator" by "Unscheduled visits may be initiated as needed. Adverse event, concomitant medication and assessment of asthma exacerbation are mandatory, and additional assessments may be performed at these visits, at the discretion of the Investigator." to emphasize the medical evaluation at unscheduled visits.
- In Section 4.1.2, removing "prior to Visit 1", as ICF date is equal to visit 1.
- In Section 4.1.3 Re-screening, replacing "Re-screening is allowed only once for the patient. Patients who experience an asthma exacerbation during the screening period may remain in screening and may proceed with study visits after they completed their course of oral steroids or returned to their maintenance dose of oral steroids. Patients with respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent, and assent when applicable is obtained or during the screening period may also be re-screened. If the reason for screen failure was transient (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits), patients may potentially be re-screened. These cases should be discussed with the AstraZeneca study physician and documented in the Investigator Study File (ISF). For those patients who were screen failed at Visit 3 or thereafter the re-screening period can be reduced. Visit 1 and Visit 2 can be done at the same day; Visit 3 can be done 1 week after Visit 2, and Visit 4 can be done 1 week after Visit 3. Re-screened patient should re-sign the informed consent, and assent when applicable on the re-screening Visit 1. All procedures from screening period should be repeated." by "Re-screening may be allowed twice for the patient screen-failed due to asthma exacerbation, otherwise re-screening is only allowed once. Patients who experience an asthma exacerbation during the screening period may remain in screening and may proceed with study visits after they completed their course of oral steroids or returned to their maintenance dose of oral steroids. Patients with respiratory infections requiring antibiotics or antiviral

medication within 30 days prior to the date informed consent, and assent when applicable is obtained or during the screening period may also be re-screened. Re-screening and/or up to 14-day extension of screening period is allowed for transient reasons (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits). These cases should be discussed with the AstraZeneca study physician and documented in the Investigator Study File (ISF). For those patients who were screen failed at Visit 3 or thereafter the re-screening period can be reduced. Visit 1 and Visit 2 can be done at the same day; Visit 3 can be done 1 week after Visit 2, and Visit 4 can be done 1 week after Visit 3. Re-screened patient should re-sign the informed consent, and assent when applicable on the re-screening Visit 1. All procedures from screening period should be repeated. A second re-screening may be allowed only when the screen failure reason was asthma exacerbation. All the cases should be discussed with the AstraZeneca study physician and documented in the Investigator Study File (ISF)." to add on one more chance for rescreening for patients screen failed due to asthma exacerbation.

- In Section 4.1.3.1, replacing "Patients who are screen-failed with an exacerbation at Visit 4 or due to exacerbation between Visit 1 and Visit 4 may be re-screened 1 time" by "Patients who are screen-failed with an exacerbation at Visit 4 or due to exacerbation between Visit 1 and Visit 4 may be re-screened 2 times" to add on one more chance for rescreening for patients screen failed due to asthma exacerbation.
- In Section4.1.3, adding "Patients with blood eosinophil number slightly <300 cell/uL at Visit 1 can be rescreened once at least 14 days later at stable stage, at the discretion of the Investigator." to introduce a single rescreening option for patients with borderline blood eosinophil levels, to improve recruitment of high eosinophil patients since the blood eosinophil fluctuate in asthma patients.
- In Section 4.2, adding "except ACQ-6". due to ACQ-6 is permitted 3 days prior to the IP injection.
- In Section 4.2, replacing "Patients who prematurely discontinued IP (see Section 3.9) and are not willing to continue to participation in the study should return to the study centre and complete procedures described for the IPD visit (Premature IP Discontinuation) and Follow-up visit within 4 weeks (+7 days) and 12 weeks (±7 days) after the last dose of IP, respectively." by "Patients who prematurely discontinued IP (see Section 3.9) and are not willing to continue to participation in the study should return to the study centre and complete procedures described for the IPD visit (Premature IP Discontinuation) within 4 weeks (+7 days, for the last dose being either the first or the second dose) or 8 weeks (+7 days, for the last dose being either the third or the following dose) and Follow-up visit within 12 weeks (±7 days, for the last dose being either the first or the second dose) or 16 weeks (±7 days, for the last dose being the third or the following dose) after the last dose of IP, respectively.", to clarify the IPD and follow-up visit timeframe and different scenarios for patients that prematurely discontinue IP.
- In Section 5.1.2, replacing "Patients should withhold their usual ICS-LABA, or LAMA medications on the morning of the screening FEV1 measurement, reversibility test (see Section 3.1, inclusion criterion 9 and 12), and all scheduled

spirometry visits. Twice daily ICS- LABA therapies should be withheld for 12- 24 hours; once daily therapies containing ICS, LABA, or LAMA therapies should be withheld for ≥24 hours before scheduled centre visit spirometry as this will affect the pre-BD FEV1 value; they may be taken subsequently, at the centre. For the same reason patients should not use their rescue SABA medication (albuterol, salbutamol or levalbuterol) within 6 hours of a scheduled centre visit spirometry. This restriction is particularly critical for efficacy measures taken during the treatment period, but should also facilitate meeting the screening reversibility eligibility criteria." by " Patients should withhold their usual ICS-LABA, or LAMA, LTRA or theophylline medications on the morning of the screening FEV1 measurement, reversibility test (see Section 3.1, inclusion criteria 9 and 12), and all scheduled spirometry visits. Twice daily ICS- LABA therapies should be withheld for 12- 24 hours; once daily therapies containing ICS, LABA, LAMA, LTRA or theophylline therapies should be withheld for ≥24 hours before scheduled centre visit spirometry as this will affect the pre-BD FEV1 value; they may be taken subsequently, at the centre. For the same reason patients should not use their rescue SABA medication (albuterol, salbutamol or levalbuterol) within 6 hours of a scheduled centre visit spirometry. This restriction is particularly critical for efficacy measures taken during the treatment period but should also facilitate meeting the screening FEV1 and reversibility eligibility criteria.", to include relevant medications (LTRA, theophylline) based on the ATS (American Thoracic Society) guideline and to align with updated eligibility criteria.

- In Section 5.1.2.1, removing "Nebulizer should not be used" to adjust to local practice.
- In Section 5.1.3, removing "(week -5)" and "Week 48", to allow flexible visit window time for Visit 2 and Visit 17.
- In Section 5.2.1, replacing "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 6.1." by "Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, as compared to the data collected at Visit 1, will be reported as an AE as described in Section 6.1.", to clarify that the visit 1 data is used to compare for new findings or aggravated existing finding(s).
- In Section 5.2.1.2, removing "For the brief physical examination only information on whether the assessment was performed or not is to be recorded.", to clarify data recording procedures.
- In Section 5.2.3, replacing "ECG data and evaluation will be recorded in the eCRF." by "ECG evaluation will be recorded in the eCRF.", to clarify that only the ECG evaluation is recorded in the eCRF.
- In Section 5.3.2.1, replacing "There will be triggers in the ePRO device to alert the patients to signs of worsening of asthma and to contact their physician, please refer to Section 5.1.1. The patient should contact the study physician for evaluation in the

setting of a diary alert." by "There will be triggers in the ePRO device to alert the patients to signs of worsening of asthma and to contact their physician in the setting of a diary alert, please refer to Section 5.1.1." to provide detail programmed information of ePRO alert for clarification.

- In Section 5.3.2.2, adding "An initial screening ACQ-6 will be taken at Visit 2 at the study centre. Between Visit 2 and Visit 3 patients will complete the ACQ-6 on a weekly basis (± 1 day)." and "Visit 2 ACQ-6 scores will determine eligibility for randomisation (see Section 3.1, inclusion criterion 16).", to keep consistency with updated eligibility criteria.
- In Section 5.3.3, replacing "At Visit 1 (Week -6) Healthcare Resource Utilization (HRU) information will be collected with a 1 year recall period. In treatment period, HRU information will be collected with a recall period of 'since last visit'.
  Note: Cases of hospitalization also must be reported as an SAE (see Section 6.2 and 6.4)." by "At Visit 1 Healthcare Resource Utilization (HRU) information will be collected with a 1 year recall period. In treatment period, HRU information will be collected with a recall period of 'since last visit'. Note: Cases of hospitalization after Visit 1 also must be reported as an SAE (see Section 6.2 and 6.4).", to clarify the procedure for the collection of HRU information and to ensure consistency in SAE reporting instructions.
- In Section 5.3.7.2, deleting "Samples retained for further use will be registered in the AstraZeneca biobank system during the entire life cycle." to align with new HGR policy.
- In Section 6.3.3, adding
  "In addition, the following variables will be collected for SAEs:

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

  to reflect the new template of AZ CSP, and also the actual data variables collected. of SAE that study is collecting.
- In Section 6.3.4, adding the new Section 6.3.4,
  "6.3.4Intensity rating scale
  1 mild (awareness of sign or symptom, but easily tolerated)
  2 moderate (discomfort sufficient to cause interference with normal activities)

3 severe (incapacitating, with inability to perform normal activities)"
to reflect the new template of AZ CSP, and clarify the definition of intensity rating scale.

- In Section 6.6.1, adding "For pregnant patients, at IPD visit, pre-BD spirometry may be skipped, at the discretion of the Investigator." to optimize the procedure for pregnant patients.
- In Section 6.61, replacing "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. "by "The PREGREP module in the CRF is used to report the pregnancy and the paper-based pregnancy outcome report is used to report the outcome of the pregnancy." to stay consistent with eCRF description.
- Adding Section 6.7 Medication error "If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day ie, immediately but no later than 24 hours of when he or she becomes aware of it. The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors. The definition of a Medication Error can be found in Appendix A." to guide the medical management of medication error.
- In Section 7.4, changing the sentence "In cases when a treatment visit cannot be scheduled within the specified window the IP administration should be skipped. If 2 consecutive dose 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;" to "In case when a treatment visit cannot be scheduled within the specified window, the investigator should discuss with AZ Study Physician to decide whether IP administration should be skipped. If 2 consecutive dose of the IP or more than 2 of the scheduled dose IP are missed during course of the study the patient should be discontinued from IP;" to make sure no IP administrations are missed during the study and to clarify when IP doses are not administered, the patient should be discontinued from IP
- In Section 7.6.1.1, adding "documented medium to high dose ICS-LABA (≥500 mcg/day fluticasone propionate dry powder formulation or equivalent daily) for at least 3 months prior to Visit 1", to keep consistency with updated eligibility criteria.
- In Section 7.6.1.1, replacing "If changing the ICS-LABA dose is judged as necessary by the Investigator, the justification should be, documented in the source and the change in the doses should be reflected in the eCRF." by "If changing the ICS-LABA dose is judged as medically necessary by the Investigator, the justification should be discussed beforehand with AstraZeneca Study Physician, documented in the source and the change in the doses should be reflected in the eCRF.", to clarify the procedure for background medication changes.
- In Section 8.1, adding "statistical analysis plan" to avoid the confusion of abbreviation and make clearer on the document name.

- In Section 8.2, replacing "The study will recruit patients with blood eosinophil counts ≥300/ μL and < 300/ μL at a ratio of about 2:1." by "The study will randomise patients with baseline blood eosinophil counts ≥ 300/ μL and < 300/ μL at a ratio of about 2:1." to clarify that the ratio is for randomised patients not for enrolled patients who just signed ICF.
- In Section 8.2, replacing "This calculation has assumed two-sided 5% alpha level tests and an annual placebo rate of 0.88 events/patient based on published data and Phase 2b MI -CP220 study interim data." by "This calculation has assumed two-sided 5% alpha level tests and an annual placebo rate of 0.88 events/patient based on published data.", to clarify that the study protocol is based on published data including Phase 2b MI -CP220 study data.
- In Section 8.3, replacing "Safety objectives will be analysed based on the Safety population." by "Safety objectives will be analysed based on the safety analysis set", as safety population is not a defined analysis set.
- In Section 8.3.2, replacing "All patients randomised and receiving any IP will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study." by "All patients who were randomised and received any IP will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study.", to correct a grammatical error.
- In Section 8.3.4, replacing
  "8.3.4Pharmacokinetic analysis set
  All patients who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations and who had at least 1 quantifiable serum PK observation post first dose will be included in the PK analysis dataset. " by
  "8.3.4Pharmacokinetic (PK) analysis set
  All patients who received benralizumab from whom PK blood samples are assumed not to be affected by factors such as protocol deviations and who had at least 1 measurable serum PK observation post first dose will be included in the PK analysis dataset. ", to clarify the PK analysis set definition.
- In Section 8.4.1.1, replacing "The primary analysis will include all available data after treatment discontinuation." by "The primary analysis will include all available data including data collected after treatment discontinuation.", to correct a grammatical error.
- In Section 8.4.1.3, replacing "The time to first asthma exacerbation for patients who do not experience an asthma exacerbation during the treatment period will be censored at the date of their last visit for the 48-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients) ." by "The time to first asthma exacerbation for patients who do not experience an asthma exacerbation during the treatment period will be censored at the date of their last visit for the 48-week treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up patients or withdrawn patients) .", to be consistent throughout study protocol.

- In Section 8.4.1.5, adding "for a patient during the 48-week double-blind treatment period" for clarity.
- In Section 8.4.2.1, replacing "Change from baseline (Visit 4) to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. AEs will be summarized by means of descriptive statistics and qualitative summaries." by "Change from baseline to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. The last non-missing measurement prior to the first dose of study treatment will serve as the baseline measurement for safety variables. AEs will be summarized by means of descriptive statistics and qualitative summaries." for safety variables, asthma symptom score, ACQ-6 and SGRQ since the baseline value may not be the Visit 4 value if a visit 4 value is not taken. A more accurate definition for baseline is added (the last non-missing measurement prior to the first dose of study treatment will serve as the baseline measurement for safety variables." or is already in the protocol (e.g. ACQ-6 and SGRQ baseline will be the last observation prior to study drug administration).
- In Section 8.4.3.4, replace "Baseline will be the 10 days prior to randomisation and will be summarized as a mean." by "Baseline will be the 14 days prior to randomisation and will be summarized as a mean." as the ePRO compliance eligibility criteria is for the last 14 days of run-in period.
- In Section 8.5, deleting "including follow-up (where applicable), unless the patient withdraws consent, and assent when applicable to study participation" to correct the confliction information.
- In Section 8.5, The covariate "country" included in the statistical models for primary and secondary endpoints is replaced by "region (China/non-China)" due to the limited number of patients in non-China countries.
- In Section 8.5.2.2, replacing "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." by "Central laboratory reference ranges will be used for the identification of abnormalities, and a shift table will be produced for each laboratory parameter to display low, normal, high, and missing values. Shifts from normal to abnormal between baseline and post-baseline will be evaluated for urinalysis. Changes in vital signs will be examined at each visit and at endpoint. Baseline to maximum post-baseline and baseline to minimum post-baseline value shift tables will be generated, as applicable for each vital signs' parameter. A shift table for ECG will be produced to display the Investigator assessment of normal, abnormal – not clinically significant, abnormal –

clinically significant and not done between baseline and end of study. No separate summaries of physical examination findings will be produced since physical examination results will be presented in Medical History and AE summaries." to be consistent with SAP and for clarity. Per SAP, the clinically noteworthy values for laboratory data and vital signs data are not defined and only abnormality is specified. The numeric result of ECG is not collected in eCRF and only the Investigator evaluation of normal/abnormal is collected. Per the eCRF, physical examination results are not collected. Physical examination is presented as AE/medical history.

- In Section 8.5.2.3, removing "Serum concentration -time profiles of benralizumab by treatment group will be generated." to clarify that PK concentration time profiles will not be generated.
- In Section 8.5.2.3, replacing "To compare the pharmacokinetics of current study with those in global pivotal studies, observed steady-state troughs will be overlaid against the 95% prediction interval generated based on final updated population PK model (see Benralizumab Population Pharmacokinetic Analysis) with significant covariates identified in the model resampled from current study." by "The population PK analysis will be presented separately from the main clinical study report (CSR).", to clarify that the results of population PK analysis will not be presented in the main CSR.
- In Section 8.5.3, replacing "To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analyses and statistical modelling including testing for interaction between treatment and covariates will be performed in patients with baseline blood eosinophil counts ≥300/ μL for the following factors: OCS use at baseline (yes/no), gender, age (<18, 18-65, and ≥65 years), country/region, BMI (≤35, >35 kg/m2), and the number of exacerbations during the previous year (2, ≥3 exacerbations), and race." by "To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analyses and statistical modelling including testing for interaction between treatment and covariates will be performed in patients with baseline blood eosinophil counts ≥300/ μL for the following factors: OCS use at baseline (yes, no), gender, age (<18, 18-65, and ≥65 years), region (China/non-China), country, BMI (≤35, >35 kg/m2), the number of exacerbations during the previous year (2, ≥3 exacerbations), the number of exacerbations during medium-high ICS/LABA treatment prior to study enrolment (2, ≥3 exacerbations), ICS dose at study enrolment (medium, high) and race." Added two subgroups related to ICS dose as the level of ICS dose (medium/high) is an important factor. Updated subgroup "country/region" to two subgroups "country" and "region (China/non-China)".
- In Section 8.6, replacing "An independent adjudication committee will be constituted to provide an independent, external, systematic, and unbiased assessment of blinded data to confirm the diagnosis of: 1) Investigator-reported non-fatal myocardial infarction, non-fatal stroke (haemorrhagic, ischemic, embolic), as well as all deaths and 2) Investigator-reported malignancies during the Phase 3 trials ." by "An independent adjudication committee will be constituted to provide an independent, external, systematic, and unbiased assessment of blinded data to confirm the diagnosis of: 1) Investigator-reported non-fatal myocardial infarction, unstable angina

, non-fatal stroke (haemorrhagic, ischemic, embolic), as well as all deaths and 2) Investigator-reported malignancies during the study.", to match the current EAC charter wording.

- In Section 9.2.2, replacing "The data will be validated as defined in the Data Management Plan." by "The data will be validated as defined in the Data Management Documentation.", to correct a grammatical error.

- In Section 9.3, replacing "The study may be terminated at individual study centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with benralizumab." by "The study may be terminated at individual study centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with benralizumab.
AstraZeneca reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:
meet individual stopping criteria or are otherwise considered significant,
are assessed as causally related to study drug,
are not considered to be consistent with continuation of the study.
Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.
In terminating the study, AstraZeneca will ensure that adequate consideration is given to the protection of the subjects' interests.
Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:
Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
Inadequate recruitment of participants by the investigator
Discontinuation of further study intervention development", to clarify more scenarios of site & study closure according to new protocol template.

- In Section 10.3, adding
"**Regulatory Reporting Requirements for SAEs according to new protocol template**

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority

and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements. "In Appendix A, replacing
"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 patient 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?
No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?
A "reasonable possibility" could be considered to exist for an AE where 1 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." by
"A GUIDE TO INTERPRETING THE CAUSALITY QUESTION
When making an assessment of causality, consider the following factors 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 patient 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?
De-challenge 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.
Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?
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?
Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship. The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.
Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.", to incorporate revised AZ SOP language.to.

- In Appendix E, replacing,

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	>250-500	>500
Fluticasone furoate (DPI)	NA	200

Budesonide	>400 to 800	>800 - 1600
Budesonide, if as delivered dose (eg Symbicort)	>320 to <640	≥640 - 1280
Mometasone furoate	>220-440	>440

by,

Asthma Therapy	Total Daily Dose (µg/day)	
Inhaled Corticosteroid	Medium	High
Beclomethasone dipropionate (CFC)	>500 - 1000	>1000 - 2000
Beclomethasone dipropionate (HFA)	>240 - 480	>480
Beclomethasone dipropionate (Fostair)	>200 - 400	>400 - 800
Budesonide	>400 to 800	>800 - 1600
Budesonide, if as delivered dose (eg Symbicort)	>320 to <640	≥640 - 1280
Ciclesonide	>160 - 320	>320 - 1280
Flunisolide	>1000 - 2000	>2000
Fluticasone propionate (DPI)	>250 - 500	>500 - 1000
Fluticasone propionate (HFA)	>250 - 500	>500
Fluticasone furoate (DPI)	NA	200
Mometasone furoate	>220-440	>440
Triamcinolone acetonide	>1000 - 2000	>2000

Note: Categories of "medium" and "high" doses are based on published information and available studies (at the time of GINA 2018 publication), including direct comparisons where available. Doses may be country-specific depending on labelling requirements. For new preparations, manufacturer's information should be reviewed carefully; products containing the same molecule may not be clinical equivalent (GINA 2018)., this update is due to update of GINA2018.

- In Appendix F, replacing table 5,

Table 5 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 PEF assessments (to be administered once assessments are completed)
Short acting beta2-agonists (SABA)	Restricted	Regular scheduled use .in the absence of any asthma symptoms and/or planned exercise is discouraged from enrolment through the study duration Rescue use of SABA administered via nebulisation is allowed 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 and oral corticosteroids)	Allowed with restriction	Have been used for 1 month prior to Visit 1; stable dose during the treatment period
Short acting anticholinergics (e.g. ipratropium)	Restricted	Not allowed from enrolment 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 Maintenance and Reliever Treatment)	Prohibited	Not allowed from enrolment and throughout the study duration
Five- lipoxygenase inhibitors (eg.Zileuton)	Prohibited	Not allowed 30 days prior to Visit 1; during treatment period

by,

Table 5 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 visit 1 and throughout the study (unless there is a medical need as judged by the Investigator and discussed beforehand with AstraZeneca Study Physician) Usual ICS-LABA should not be taken prior to scheduled spirometry, ECG and home PEF assessments (to be administered once assessments are completed)
Short acting beta2-agonists (SABA)	Restricted	Regular scheduled use in the absence of any asthma symptoms and/or planned exercise is discouraged from Visit 1 throughout the study. Rescue use of SABA administered via nebulisation is allowed. 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 and oral corticosteroids)	Restricted	Have been used for at least 1 month prior to Visit 1; stable dose during the treatment period. Usual controller should not be taken prior to scheduled spirometry, ECG and home PEF assessments (to be administered once assessments are completed).

Short acting anticholinergics (e.g. ipratropium)	Restricted	Not allowed from Visit 1 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 Maintenance and Reliever Treatment)	Prohibited	Not allowed from Visit 1 and throughout the study duration
Five- lipoxygenase inhibitors (eg.Zileuton)	Prohibited	Not allowed 30 days prior to Visit 1; during treatment period

The changes are to correct some previous errors and rephrase some wording.

- In Appendix F, adding "Usage of the following restricted medications might be acceptable for AE treatment after discussion with AstraZeneca Study Physician." to clarify the exceptional case of using restricted medication exceptions.
- In Appendix F, table 6, replacing,

Table 6 Other medication restrictions

Medication	Prohibited/restricted	Details
Live Attenuated Vaccines	Prohibited	Not allowed 30 days prior to randomisation; during treatment period, and 16 weeks (5 half-lives) after the Last Dose of the investigational product
Inactive/killed vaccinations (e.g. inactive influenza)	Restricted	Allowed provided they are not administered within 1 week before/after any IP administration.
Any immunomodulator or Immunosuppressive	Prohibited	Not allowed within 3 months prior to the date informed consent is obtained; during treatment period; 3 Months or 5 Half Lives (whichever is longer) after

		Last Dose
Any immunomodulators or immunosuppressives – topical	Restricted	Topical administration of immunosuppressive medication may be allowed at the discretion of the Investigator after discussion with the AstraZeneca Study Physician
Blood products or immunoglobulin therapy	Prohibited	Not allowed 30 days prior to date of ICF; during treatment period
Any marketed (eg omalizumab) or investigational biologic treatment	Prohibited	Not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1; during treatment period; 4 months or 5 half-lives (whichever is longer) after the last dose of the investigational product
Other investigational Products (including investigational use of an approved drug)	Prohibited	Not allowed 30 Days or 5 Half Lives (whichever is longer) prior to randomisation; during treatment period
Allergen Immunotherapy	Restricted	Allowed if on stable therapy, or stable seasonal therapy, for at least 30 days prior to date of ICF; Immunotherapy injections must be separated from IP injections by at least 7 calendar days
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases	Prohibited	Not allowed 30 days prior to Visit 1; during treatment period
Roflumilast	Prohibited	Not allowed 30 days prior to Visit 1; during treatment period
Non-selective oral or ophthalmic β-adrenergic antagonist (e.g. propranolol)	Prohibited	Patients currently using any non-selective oral or ophthalmic β-adrenergic antagonist at

		the time of enrolment are not eligible for the study. Not allowed during treatment period.
Medications not currently licensed for use in the treatment of asthma and not part of current standard of care	Prohibited	Not allowed within 30 days prior to randomisation; throughout the duration of the study

by,

Table 6 Other medication restrictions

Medication	Prohibited/restricted	Details
Live Attenuated Vaccines	Prohibited	Not allowed 30 days prior to randomisation; during treatment period, and 16 weeks after the Last Dose of the investigational product
Inactive/killed vaccinations (e.g. inactive influenza)	Restricted	Allowed provided they are not administered within 1 week before/after any IP administration.
Any immunomodulators or Immunosuppressives	Prohibited	Not allowed within 3 months or 5 Half Lives (whichever is longer) prior to the date informed consent is obtained; during treatment period; 3 Months after Last Dose
Any immunomodulators or immunosuppressives – topical	Restricted	Topical administration of immunosuppressive medication may be allowed at the discretion of the Investigator after discussion with the AstraZeneca Study Physician
Blood products or immunoglobulin therapy	Prohibited	Not allowed 30 days prior to date of ICF; during treatment period.

Any marketed (eg omalizumab) or investigational biologic treatment	Prohibited	Not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1; during treatment period; 16 weeks 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 randomisation; during treatment period; and 16 weeks after the last dose of the investigational product
Allergen Immunotherapy	Restricted	Allowed if on stable therapy, or stable seasonal therapy, for at least 30 days prior to date of ICF; Immunotherapy injections must be separated from IP injections by at least 7 calendar days
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases	Prohibited	Not allowed 30 days prior to Visit 1; during treatment period
Roflumilast	Prohibited	Not allowed 30 days prior to Visit 1; during treatment period
Non-selective oral or ophthalmic β-adrenergic antagonist (e.g. propranolol)	Prohibited	Patients currently using any non-selective oral or ophthalmic β-adrenergic antagonist at the time of Visit 1 are not eligible for the study. Not allowed during treatment period.
Medications not currently licensed for use in the treatment of asthma and not part of current standard of care	Prohibited	Not allowed within 30 days prior to randomisation; throughout the duration of the study

Those changes are to clarify the time period of prohibited medication and to correct grammatical errors.

• In the whole protocol, replacing "randomization" by "randomisation" to keep consistency.
Version 3.0, 25 Apr 2018 Changes to the protocol are summarised below:
The main purpose of the Version 3 protocol change is the patient sample size reduction and to provide clarifications throughout the protocol. • **In Protocol Synopsis, Section 1.4**, replacing "Approximately 834 patients will be randomised, among which at least 666 (333 patients/arm) patients will be recruited from China" by "Approximately 666 patients will be randomised, among which approximately 534 (267 patients/arm) patients will be recruited from China" due to patient sample size change. The change will still provide adequate power for efficacy and solid safety data. • **In Protocol Synopsis, Section 1.4, Section 3.3, Section 3.10.2,** replacing "bullet 1. The eosinophil <300/μL stratum will be closed to all the patients from China when the total number of Chinese patients in the stratum reaches approximately 222." with "bullet 1. The eosinophil <300/μL stratum will be closed to all the patients from China when the total number of Chinese patients in the stratum reaches approximately 178." due to patient sample size change. • **In Protocol Synopsis, Section 1.4, Section 3.3 and Section 3.10.2 and Section 8.2,** replacing "bullet 2. The eosinophil <300/μL stratum will be closed to the patients from all countries when the total number of patients in the eosinophil <300/μL stratum reaches approximately 278." by "bullet 2. The eosinophil <300/μL stratum will be closed to the patients from all countries when the total number of patients in the eosinophil <300/μL stratum reaches approximately 222" due to patient sample size change. • **In Protocol Synopsis, Section 1.4 and Section 3.10.2,** replacing "Bullet 3. The eosinophil ≥300/μL stratum will be closed to all the patients from China when the

total number of Chinese patients in the stratum reaches approximately 444." by "bullet 3. The eosinophil ≥300/μL stratum will be closed to all the patients from China when the total number of Chinese patients in the stratum reaches approximately 356." due to patient sample size change.

- **In Protocol Synopsis, Section 1.4 and Section 3.10.2,** replacing "Bullet 4. The whole study will be closed for recruitment when the total number of patients in the eosinophil ≥300/μL stratum reaches approximately 556." by "Bullet 4. The whole study will be closed for recruitment when the total number of patients in the eosinophil ≥300/μL stratum reaches approximately 444" due to patient sample size change.
- **In Protocol Synopsis and Section 1.4,** replacing "from enrolment throughout the run in and treatment period" by "from visit 1 until the end of the study." The updated approach will be consistent with the protocol section 7.6.1.1 that all patients are required to be treated with medium to high dose ICS-LABA for at least 6 months prior to Visit 1 and during the study.
- **In section 1.4,** replacing "Patients will be maintained on their currently prescribed high-dose ICS- LABA therapy(ies)." by" Patients will be maintained on their currently prescribed medium to high-dose ICS- LABA therapy," to keep consistency with section 7.6.1.1
- **In section 3.1, inclusion criteria 1,** replacing "according to international guidelines and/or applicable European Union guidelines" by "according to international guidelines and/or applicable local guidelines". As no European Union countries participate in this study.
- **In section 3.1, inclusion criteria 4,** replacing "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" by "4. All male patients who are sexually active should agree to use an adequate method of contraception (condom or condom with spermicide depending on local regulations) from the first dose of IP until 16 weeks after their last dose" The update is to provide flexibility in countries where condom with spermicide are not widely available.
- **In section 3.1, inclusion criteria 6,** replacing "6. History of physician-diagnosed asthma requiring treatment with medium-to-high dose ICS (>250μg fluticasone dry powder formulation equivalents total daily dose) and a LABA, for at least 6 months prior to Visit 1." by "History of physician-diagnosed asthma requiring treatment with medium-to-high dose ICS (>250μg fluticasone propionate dry powder formulation equivalents total daily dose) and a LABA, for at least 6 months prior to Visit 1." The update is to clarify the equivalence dose should be calculated according to fluticasone propionate rather than fluticasone furoate.
- **In section 3.2, exclusion criteria 17,** deleting "within 4 months or within 5 half-lives prior to the date informed consent and assent is obtained, whichever is longer" As this requirement is only applicable to European Union countries and not applicable to MIRACLE study.

- **In section 3.2, exclusion criteria 24,** replacing "Concurrent enrolment in another clinical trial" by "Participation in another clinical investigational study." The change is to follow the new protocol template and allowing the patient to join observational studies.
- **In section 3.6,** deleting "double dummy" within "The study will be conducted in double-blind, double dummy fashion", the revision is to correct the error that this is not double dummy study.
- **In section 3.6,** replacing "In cases where the Investigator requires an eosinophil, basophil or monocyte count for managing safety issues, AstraZeneca physician should be notified of all such cases" by "In cases where the Investigator requires an eosinophil, basophil or monocyte count for managing safety issues, AstraZeneca physician should be notified of all such cases, without being revealed the eosinophil, basophil or monocyte count". The revision is to emphasize the requirement to keep AZ physician as blind.
- **In section 3.8.1, section 4.1.2 and Table 1 footnote f),** deleting "or FEV1 (<80% or <90%) criteria". The revision is to correct that FEV1 (<80% or <90%) is not the eligibility criteria.
- **In section 3.8.2,** deleting "or administration of live/attenuated vaccines", as this requirement has been included in section (b) that "Receipt of live attenuated vaccines within 30 days prior to randomisation, during the treatment period, and for 16 weeks (5 half-lives) after the last dose of the IP is not allowed."
- **In section 3.10.4,** deleting "If the patient only withdraws consent, and assent when applicable, for the retention of samples for future exploratory use (e.g. study of markers of asthma, identifying potential new drug targets for asthma, or for assay development purposes), samples will not be withdrawn from the study." The deletion is due to samples will not be retained for future exploratory use.
- **In section 4.1.1,** deleting "Those procedures must be initiated within 3 working days from the date of ICF." The revision is to clarify that visit 1 is equal to the date of ICF, and all procedures should be initiated after the date of ICF and to be completed before visit 2.
- **In section 4.1.2 and Table 1 footnote b),** replacing "Visit 3 can be performed within 1 week before Visit 4 or on the same day as Visit 4. If Visit 3 and Visit 4 are combined then all procedures from both visits should be done. On Visit 3 ACQ-6 will be recorded (for baseline purposes only). Patient's eligibility should be evaluated at each visit during the run-in period with the relevant documentation entered in the source and eCRF" by "Visit 3 can be performed within 1 week before Visit 4. Visit 3 and Visit 4 may take place on the same day only for well characterized patients (those who did not have lab results outside the normal range at Visit 1 for parameters associated with eligibility criteria (eg Liver Function Tests) as any such results should be retested, with results available before randomisation, in order to ensure patient eligibility is not affected. If Visit 3 and Visit 4 are combined then all procedures from

both visits should be done. On Visit 4, ACQ-6 will be recorded (for baseline purposes only). Patient's eligibility should be evaluated at each visit during the run-in period with the relevant documentation entered in the source and eCRF". The revision is to clarify the requirement of combining these two visits, and to correct the visit number for ACQ-6 recording.

- **In section 5.1.2,** deleting "within 30±15 minutes" from "procedures should commence within 30±15 minutes according to the regimen for reversibility testing outlined in Section 5.1.2.1". The deletion is to keep consistency with the Figure 2 in section 5.1.2.1.

  In section 5.1.2, adding "and IP" for "Order of administration of usual asthma controller medication and IP relative to scheduled pre-bronchodilator spirograms" The revision is to provide clarity.

- **In section 5.1.2.1,** replacing "meets ATS (American Thoracic Society) criteria (12% and 200 mL)" by "meets inclusion criteria (≥12% and ≥200 mL)" within the sentence "If a reversibility maneuver that meets inclusion criteria (≥12% and ≥200 mL) is rejected as the best maneuver after central revision, it may still be used to satisfy Inclusion Criterion 7. "The revision is to keep consistency with eligibility criteria, which is not exactly the same with ATS criteria
- **In section 5.1.3,** replacing "evening of Visit 2 (Week -3)" by "evening of Visit 2 (Week -5)" to keep consistency with the visit window.
- **In section 5.2.3,** deleting" two identical copies of the" within the sentence "two identical copies of the ECG will be produced and quality checked and kept in case of further need for re-evaluation" The deletion is due to operational complexity.
- **In section 5.3.2.2,** replacing "every 4 weeks (±1day) until Week 8 and then once every 8 weeks (±1day) throughout the treatment period until Week 48." by "every 4 weeks (±3day) until Week 8 and then once every 8 weeks (±3day) throughout the treatment period until Week 40. Patients will be asked to complete the ACQ-6 at EOT, Week 48 (+7day) or IPD visit" The revision is to keep consistency with the visit window.
- **In section 5.3.3,** replacing "Subsequent visits will collect HRU information with a recall period of 'since last visit'" by "In treatment period, HRU information will be collected with a recall period of 'since last visit'." The revision is to provide clarity.

  In section 5.3.5 and section 5.3.6, replacing "The PK and immunogenicity samples may be retained for future use at AstraZeneca or designee for a maximum of 15 years or as per local regulations from the date of the Last Patient's Last Visit, after which they will be destroyed." by "After primary bioanalysis, residual PK and immunogenicity sample aliquots may be retained for the purposes of re-analysis at AstraZeneca or designee for a maximum of 5 years after publication of the Clinical Study Report or per local regulations, after which they will be destroyed. This is intended to allow AstraZeneca to investigate any anomalous results or respond to

regulatory authority questions. Samples will only be re-analysed according to the original purpose for which they were collected (e.g. PK or immunogenicity analysis)." The revision is due to samples not being retained for future exploratory use and add the requirement to meet the purpose of re-analysis.

- **In section 5.3.7.2,** deleting "Samples retained for further use will be registered in the AstraZeneca biobank system during the entire life cycle." The deletion is due to samples not being retained for future exploratory use.

- **In section 6.3.8,** replacing "The patient discontinues the study due to the sign or symptom" by "The patient discontinues the IP due to the sign or symptom." The revision is due to AEs leading to discontinuation of IP, rather than discontinuation of study. Patient is encouraged to stay in study even if the IP were to be discontinued.

- **In section 8.4.3.4**, replacing "Baseline will be the 14 days prior to randomisation and will be summarized as a mean" by "Baseline will be the 10 days prior to randomisation and will be summarized as a mean." The revision is to keep consistency with section 5.1.1 Assessment of asthma exacerbations.

- **In section 8.5.2,** adding "and asthma symptom control status at EOT" after "i.e. baseline to EOT ACQ-6 score change of ≥ -0.5 points" within the sentence "The ACQ-6 will be analysed in terms of change from baseline to end of treatment, change from baseline to overall post-baseline mean, and responder status at EOT (i.e. baseline to EOT ACQ-6 score change of ≥ -0.5 points), and asthma symptom control status at EOT." The revision is to keep consistency with section 5.3.2.2 and 8.4.3.2.

- **In section 8.6,** replacing "cardiovascular deaths" to "all deaths" within the sentence 1) Investigator-reported non-fatal myocardial infarction, non-fatal stroke (haemorrhagic, ischemic, embolic), as well as all deaths. The revision is due to additional attention required for all death events.

- **In Appendix E,** replacing

Asthma Therapy	**Total Daily Dose (µg/day)**	
Inhaled Corticosteroid	Medium	**High**
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	≥800

to:

Asthma Therapy	**Total Daily Dose (µg/day)**	
Inhaled Corticosteroid	Medium	**High**
Fluticasone propionate HFA	>250-500	>500

Fluticasone furoate (DPI)	NA	200
Budesonide	>400 to 800	>800 - 1600
Budesonide, if as delivered dose (eg Symbicort)	>320 to <640	≥640 - 1280
Mometasone furoate	>220-440	>440

The revision is to update according to GINA 2017.

- **In Appendix F,** deleting "PROHIBITED AND RESTRICTED MEDICATIONS" due to duplicate information.
- **In Appendix F,** Live attenuated Vaccines, replacing "4 months" to "16 weeks" in the sentence "Not allowed 30 days prior to randomisation; during treatment period, and 4 months (5 half-lives) after the Last Dose of the investigational product. The revision is to keep consistency with revised exclusion criterion 17.
- **In Appendix F,** the investigational Products (including investigational use of an approved drug), replacing "Visit 1" to "randomisation" in the sentence "Not allowed 30 days prior to randomization; during treatment period, and 4 months (5 half-lives) after the Last Dose of the investigational product". The revision is to keep consistency with revised section 3.8.2 (b).
- Correct several typos and administrative changes throughout the CSP.

Version **2.0, 28Nov2016**

Changes to the protocol are summarised below:

The main purpose of the Version 2 protocol changes is to optimize the eligibility criteria and adapt changes following the global pivotal study D3250C00017 (Bleecker et al 2016).

- In **Protocol Synopsis, Section 1.2, 1.4, 8.5.3**, replacing "*geographical region*" by "country/region" as one of the stratification factors.
- In **Protocol Synopsis, Section 1.4**, the dose included in this protocol is Q8W. Removing all Q4W, Q8W wordings to avoid confusion and replacing with "Every 4 weeks for first 3 doses, then every 8 weeks thereafter".
- In **Protocol Synopsis, Section 1.4, Table 1, 4.1.2**, Prolonged the Run-in period from 2~3 weeks to 4~5 weeks. This requirement is to make sure the asthma is uncontrolled (assessed by symptom score within 7 days prior to Randomisation) despite of treatment of medium-to-high dose ICS/LABA.
- In **Protocol Synopsis, Section 2.2, Table 1, Section 4.2, 5.3.2.2, 5.3.2.3, 8.4.3.3, 8.4.3.4, 8.5.2,** Use SGRQ to assess health-related quality of life (HRQoL) to replace the AQLQ(s)+12. The SGRQ is a more suitable assessment of HRQoL in severe asthma patients when compared with the AQLQ(s)+12.

- In **Protocol Synopsis, Section 2.3,** removing the "Physical Examination" as one of the safety objectives, because no Physical Examination results will be collected in eCRF. Clinically significant changes of physician examination would be reported as adverse event.
- In **Section 1.1.2**, Added results from global pivotal studies (Bleecker et al 2016, FitzGerald et al). "……In the pivotal studies, compared with placebo, benralizumab 30 mg administered subcutaneously (benralizumab 30 mg every 4 weeks for the first 3 doses and then every 8 weeks thereafter) significantly reduced the annual asthma exacerbation rate, improved asthma symptom and lung function (prebronchodilator FEV_1). The purpose of this trial is to confirm the efficacy and safety of benralizumab administration in asthma patients who are otherwise uncontrolled on current standard of care therapy. The question of the baseline blood eosinophil level that predictably ensures the clinical benefit in patients will also be addressed in the study by inclusion of patients with blood eosinophil counts ≥300/μL and <300/μL.".
- In **Section 3.1, Inclusion criteria 8**, to add restriction on the asthma exacerbation documentation, adding sentence of "at least 1 of the 2 exacerbations should occur during the treatment of medium-to-high dose ICS-LABA".
- In **Section 3.1, Inclusion criteria 13**, for sentence "At least 70% compliance with usual asthma controller ICS-LABA during over the 14 days prior to randomisation based on Asthma Daily Diary.", using "during over the 14 days prior to randomisation" replace the original 'during run-in period (from Visit 2 to Visit 4)' because the run-in period is now minimal 4 weeks instead of original 2 weeks.
- **In Section 3.1, Inclusion criteria 14**, removing "*Minimum 80% compliance with ePRO completion - 80% compliance defined as completing Asthma Daily Diary for any 8 mornings and any 8 evenings of the last 10 days of the run-in period*", **and replace with** "At least 70% compliance with ePRO completion - At least 70% compliance defined as completing Asthma Daily Diary for any 10 complete days (i.e., consecutive evening and morning, for example, Day -14 evening + Day -13 morning) of the last 14 days of the run-in period." The updated approach will be consistent with the post-baseline evaluation.
- In **Section 3.2**, combine exclusion criteria #19 and #24 for simplicity. Revised as "Previously randomised in any benralizumab (MEDI-563) study, including the present study.".
- In **Section 3.2**, add the exclusion criterion #30, "Received bronchial thermoplasty (BT) as treatment of asthma within 12 months prior to Visit 1", because BT is common in several sites in China and would impact the efficacy assessment.
- In **Section 3.2**, for exclusion criteria #18, add "Use of any off-label medications, for example medications locally approved for Chronic Obstructive Pulmonary Disease but not for asthma, are also not allowed from 30 days prior to randomisation and throughout the study." following changes from global pivotal study SIROCCO, to further clarify this criterion.

- In **Section 3.6**, removing below paragraph due to operational complexity. "***Handling of labs obtained during the treatment period but ordered outside of the clinical trial***. Centre staff who are directly involved in the patient's management should remain blinded to any eosinophil, basophil and monocyte results included as part of outside lab reports. To help ensure this, each investigational centre will designate an individual (eg, administrator or another ancillary person) not directly involved in patient management, to receive and blind any eosinophil, basophil, and monocyte results prior to the report being handed over to the centre staff involved in the patient's management and prior to filing as a source document. Similarly, eosinophil and basophil results must be redacted from all communications with the Sponsor.".
- In **Section 3.6**, removing below paragraph to the 1st bullet in the section: "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.".
- In **Section 3.8.1**, delete the paragraph of "Patients on theophylline should have blood concentration levels checked, assessed and documented prior to randomisation. The theophylline level must not exceed the upper limit of the therapeutic range.", in **Section 3.8.2,** delete the paragraph of bullet (d), "When enrolling a patient who is on theophylline, digoxin or other drugs with a narrow therapeutic range, the Investigator should ensure the levels of each of these medications must not exceed the upper limit of therapeutic range. The Investigator will also be responsible for ensuring that these levels are regularly checked, assessed and documented as per local practice (see Table 1)", and in **Section 4, Table 1,** removing "blood concentration" in Enrolment visit, and in **Section 5.2.4, Table 3,** removing "serum concentration". The above changes are to improve the feasibility and simplify the procedure. Instead, the Investigator will regularly monitor vital signs, ECG, and AE to assess subjects' safety.
- In **Section 4, Table 1,** to keep consistence with section 4.1.2, "[a] All visits are to be scheduled from the date of randomisation but not from the date of previous visit.", are replaced with "[a] Visit 2 may take place as soon as medication restrictions prior to spirometry/reversibility tests are met (see Section 3.8), and should occur no later than 1 week after Visit 1. Visit 2 procedures may be performed on the same day as Visit 1 if the medication restriction is met.".
- In **Section 4, Table 2,** Change clinic visit to phone visit at W12, 20, 28, 36 and 44 (the visits between contiguous IP dosing), to simplify the protocol, meanwhile still can assess efficacy (exacerbation) and safety (AE, concomitant medication). Removing the tests for "Brief physical examination", "Vital Signs", "Urine pregnancy test", ACQ-6 adherence at W12, 20, 28, 36 and 44 to keep consistence.
- In **Section 4, Table 2,** removing the PK sampling at W8, W56 and ADA/nAb sampling at W56. Benralizumab PK has been extensively evaluated in global phase 3 programs. The steady-state PK will be sufficient for comparison with global outcome for bridging. ADA sample collection will be reduced to keep consistence with PK time points.

- In **Section 4, Table 2, Section 5.3.5,** removing "Immunoglobulins (IgE)" related wording and paragraph which is not necessary for this study.
- In **Section 4, Table 2, Section 5.4.2.1,** for "Urine pregnancy test", removing "dipstick" to use site local lab providing sourcing data for possible regulatory inspection in China.
- In **Section 4, Table 2, Section 5.3.6** "**Neutralizing antibodies**", **Section 8.4.5**, replacing the sentence "Neutralized antibodies (nAb) is to be tested at all ADA collection time points of Week 16 and later in samples that are ADA positive. Samples that are ADA negative will not be tested for nAb." with "All ADA positive samples will be tested for neutralizing antibodies (nAb)." to follow changes from global pivotal study SIROCCO amendment 2 and clarify the time points of the samples that will be tested for nAb.
- In **Section 5.1.2**, removing "IP dosing should also be withheld until pre-bronchodilator spirometry is complete" to follow changes from global pivotal study SIROCCO amendment 1. The amendment allowing sites the option of performing spirometry after the IP injection will shorten the duration of injection day visits to accommodate patient schedules, meanwhile will not impact the assessment of lung function.
- In **Section 5.2.4, Table 4,** removing the whole Table 4 as it is necessary to have full panel lab tests taken at all the visits to track the patient safety.
- In **Section 5.3.2.2, Asthma control questionnaire (ACQ-6)**, removing ACQ-6 assessments at phone visits (i.e., remove ACQ-6 assessments at W12, W20, W28, W36, and W44).
- In **Section 7.4,** removing "The patient, in the opinion of the Investigator, is experiencing an acute or emerging asthma exacerbation", following changes from global pivotal study SIROCCO amendment 2. The Investigator will determine if the visit should be rescheduled and IP administration withheld in the event the patient is experiencing an acute or emerging asthma exacerbation. Worsening asthma, in and of itself, is not a reason to not administer IP.
- In **Section 7.6.1.1**, **Background medication,** to add "<u>medium to high dose</u>" for ICS covering both adult and adolescent patients, and revise the duration for ICS, LABA treatment to at least 6 months prior to Visit 1 and during the study.
- In **Section 7.7,** revision following changes from global pivotal study SIROCCO amendment 2, to allow more flexibility with the timing of the blood draw for additional ADA testing.
- In **Section 8.4.2.2,** removing this whole section related to OAE (other significant AEs), to keep consistence with global pivotal studies.
- **In Section 8.4.3.4**, **removing** "Baseline is defined as the last non-missing value before randomisation for the asthma PROs and as the last 10 days before randomisation for the daily metrics. Each post-randomisation period is defined as the period between 2 consecutive scheduled visits (till Week 48 Visit). The change from

baseline to each post-randomisation period will be used as secondary efficacy variables." **and replacing with** "Biweekly (14 days) means will be calculated for daily assessments of asthma symptoms, night time awakenings, rescue medication usage and peak flow. Baseline will be the 14 days prior to randomisation and will be summarized as a mean. Post-randomisation biweekly (14 day) means will be calculated for each daily assessment and then summarized as group means for each 14-day period post-randomisation. ACQ-6 and SGRQ baseline will be the last observation prior to study drug administration and summarized as mean scores for each group. The change from baseline to each post-randomisation period will be used as secondary efficacy variable." The updated approach will be consistent with the post-baseline evaluation.

- In **Section 8.5.2.1,** add "Change from baseline in" before "Total rescue medication use (average puffs/day)" and "Number of nights with awakening due to asthma and requiring rescue medication", following changes from global pivotal study SIROCCO amendment 2, to clarify a change in analysis of these secondary objectives.
- In **Section 8.5.2.1,** removing "The number of nights with awakening due to asthma and requiring rescue medication will be analysed as the response variable by fitting an ANCOVA model to data. Treatment group will be fitted as the explanatory variable, and country, baseline value, the use of maintenance oral corticosteroids (yes/no) will be fitted as covariates. Total rescue medication use (average puffs/day) will be analysed using a similar model." , and replacing with "Change from baseline in total rescue medication use (average puffs/days) and number of nights with awakening due to asthma and requiring rescue medication will be analysed using a similar model as for change from baseline in pre-BD FEV1." following changes from global pivotal study SIROCCO amendment 2, due to multiple post-baseline measurements, these endpoints will now be analysed using a repeated measures model.
- In **Section 8.5.2.1,** replacing "by fitting an ANCOVA model with treatment, country, number of exacerbations in the year before the study, and the use of maintenance oral corticosteroids (yes/no) as covariates" with "using a similar model as for change from baseline in pre-BD FEV1", following changes from global pivotal study SIROCCO amendment 2, due to multiple post-baseline measurements, these endpoints will now be analysed using a repeated measures model.
- In **Section 8.5.2.1,** removing "number of exacerbations in the year before the study", following changes from global pivotal study SIROCCO amendment 2, the number of exacerbations in the year before the study was included in model in error.
- In **Section 8.6,** removing the whole paragraph of "**Independent adjudication committee**" for asthma-related exacerbation, because there is no mismatch between reported exacerbations and adjudicated exacerbations in global pivotal studies, and that there is already clear definition of exacerbation in the protocol. Investigators should be able to make the judgement.
- In **Section 8.6,** replacing the whole paragraph of "**Independent adjudication committee**" **with** paragraph of "**Independent adjudication committee for major adverse cardiac events and malignancies** An independent adjudication committee

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

- In **Section 9.4**, replacing "AstraZeneca Drug Dictionary" with "WHO Drug Dictionary" per new process, and made some revision per new template wording.
- **Appendix F (**Restricted and prohibited medications**, Appendix G in Version 1 protocol**), updated following global pivotal study SIROCCO.
- Correct a few typos throughout the CSP.
- Changes made across the CSP due to the template revamp (refer to below table for the comparison of old and new Version 17 CSP template).

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