AstraZeneca

Revised Clinical Study Protocol	
Drug Substance	Benralizumab (MEDI-563)
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A Randomised, Double-blind, Double Dummy, Chronic Dosing (56 week) Placebo-controlled, Parallel Group, Multicentre, Phase III Study to Evaluate the Efficacy and Safety of 3 Doses of Benralizumab (MEDI-563) in Patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) with a History of COPD Exacerbations (TERRANOVA)

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The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	22 April 2014		
2	10 February 2015		
3	03 July 2015		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change

PROTOCOL SYNOPSIS

A Randomised, Double-blind, Double Dummy, Chronic Dosing (56 week) Placebo-controlled, Parallel Group, Multicentre, Phase III Study to Evaluate the Efficacy and Safety of 3 Doses of Benralizumab (MEDI-563) in Patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) with a History of COPD Exacerbations (TERRANOVA)

International Co-ordinating Investigator

Redacted

Study centre(s) and number of subjects planned

Approximately 380 study centres worldwide in 24 countries will randomise a total of 2168 subjects.

Study period		Phase of development
Estimated date of first subject enrolled	Q2 2014	Phase III
Estimated date of last subject completed	Q4 2017	

Objectives

(a)   Primary Objective

Primary Objective:	Outcome Measure:
To evaluate the effect of three doses of benralizumab on COPD exacerbations in subjects with moderate to very severe COPD	Annual COPD exacerbation rate, where a COPD exacerbation is defined by symptomatic worsening of COPD requiring: • Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids; and/or • Use of antibiotics; and/or • An inpatient hospitalization or death due to COPD

(b)   Secondary Objectives

Secondary Objective:	Outcome Measure:
To evaluate the effect of three doses of benralizumab on health status/health-related quality of life	• St. George's Respiratory Questionnaire (SGRQ)* • COPD assessment tool (CAT)
To evaluate the effect of three doses of benralizumab on pulmonary function	Pre-dose/pre-bronchodilator Forced expiratory volume in one second (FEV_1)* at the study centre
To evaluate the effect of three doses of benralizumab on respiratory symptoms	• Baseline/Transitional Dyspnea Index (BDI/TDI) • Exacerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms (E-RS)
To evaluate the effect of three doses of benralizumab on nocturnal awakenings	Number of nights with awakening due to COPD

Secondary Objective:	Outcome Measure:
To evaluate the effect of three doses of benralizumab on rescue medication use	Total rescue medication use (average puffs/day)
To evaluate the effect of three doses of benralizumab on the severity, frequency and duration of EXACT-PRO defined events.	Exacerbations of Chronic Pulmonary Disease Tool – Patient-reported Outcome (EXACT-PRO)
To evaluate the effect of three doses of benralizumab on other parameters associated with COPD exacerbations	Time to first COPD exacerbation and proportion of subjects with ≥1 COPD exacerbation
To evaluate the effect of three doses of benralizumab on COPD exacerbations involving emergency room visits and hospitalizations	Annual rate of COPD exacerbations that are associated with an emergency room visit or a hospitalization
To evaluate the effect of three doses of benralizumab on health care resource utilization due to COPD	Annual rate of hospitalizations due to COPD; annual rate of hospitalizations and emergency department visits combined due to COPD; annual rate of unscheduled outpatient visits including unscheduled visits to study centres due to COPD; and annual rate of unscheduled healthcare encounters due to COPD
To evaluate the pharmacokinetics and immunogenicity of three doses of benralizumab	• PK parameters • Anti-drug antibodies (ADA)

* Key secondary efficacy endpoint

(c)   Safety Objective

Safety Objective:	Outcome Measure:
To evaluate the safety and tolerability of three doses of benralizumab	• Adverse events/Serious adverse events (AE/SAE) • Laboratory variables • 12 lead Electrocardiogram (ECG) • Physical Examination • Vital Signs

(d)   Exploratory Objectives

Exploratory Objective:	Outcome Measure:
To evaluate the effect of three doses of benralizumab on general health status	European Quality of Life-5 Dimensions (EQ-5D-5L)
To evaluate the impact of three doses of benralizumab on blood eosinophil levels	Blood eosinophils
To evaluate the effect of three doses of benralizumab on blood biomarkers	Serum biomarkers
To evaluate the effect of three doses of benralizumab on patient and physician global assessments	PGIC and CGIC
To understand the dose response relationship across a broad range of doses	Primary and key secondary endpoints across 3 benralizumab dose levels (10mg, 30mg, and 100mg).
To evaluate the effect of three doses of benralizumab on all cause and respiratory related mortality	Mortality rate

Study design

This is a randomised, double-blind, double dummy, placebo-controlled, parallel group, multicentre, phase III study to evaluate the efficacy and safety of benralizumab (MEDI-563), 10mg, 30mg and 100mg dose administered by subcutaneous (SC) injection every 4 weeks for the first 3 doses and then every 8 weeks thereafter with the last dose of IP administered at week 48 and last treatment evaluation performed at week 56, in subjects with moderate to very severe COPD receiving standard maintenance therapy (inhaled corticosteroid/long-acting $\beta2$ agonist (ICS/LABA), long-acting $\beta2$ agonist /long acting muscarinic antagonist (LABA/LAMA) or ICS/LABA/LAMA) with a history of COPD exacerbation(s) in the year prior to enrolment (Visit 1).

The study will recruit approximately 2168 subjects randomised 1:1:1:1 to the treatment arms, stratified by country and blood eosinophil count ($\geq300/\mu L$ and $<300/\mu L$ strata). The subject recruitment will be capped at the study level for the cohorts with baseline eosinophil counts $<220/\mu L$, $220-299/\mu L$, and $\geq300/\mu L$ in order to keep predefined cohort sample size and approximately 2:1 ratio of subjects above and below the boundary of $220/\mu L$. Details of the estimated numbers of recruited subjects/arm in each cohort ($<220/\mu L$, $220-299/\mu L$, $\geq300/\mu L$) are described in the SAP.

The investigational product (IP) will be administered at the study centre every 4 weeks for the first 3 doses, and then every 8 weeks thereafter, the last dose will be given at week 48 and the last treatment evaluation will be performed at week 56.

After the initial enrolment period and confirmation of the entry criteria, subjects will proceed to the screening/run-in period for 3 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Subjects who meet all the eligibility criteria will be randomised to a 56-week treatment period, with the last dose of benralizumab/placebo administered at week 48. The end of treatment (EOT) visit will occur at week 56. Subjects will be maintained on their currently prescribed maintenance therapies, from enrolment throughout the run-in and treatment period.

Final follow-up visit will be conducted at week 60. For discontinuation procedures refer to section 3.6.1.

Target subject population

Male and female subjects between 40 to 85 years of age inclusive, with a diagnosis of COPD, post-bronchodilator $FEV_1>20\%$ and $\leq65\%$ of predicted normal value, Modified Medical Research Council (mMRC) score ≥1, and history of ≥2 moderate COPD exacerbations (i.e. treated with systemic steroids and/or antibiotics) or ≥1 severe exacerbation (i.e. requiring COPD related hospitalization) in the previous year, willing to provide informed consent and requiring maintenance treatment with double (ICS/LABA, LABA/LAMA) or triple (ICS/LABA/LAMA) therapy.

Investigational product, dosage and mode of administration

Benralizumab 20mg/mL, 30mg/mL or 100mg/mL solution for injection in two accessorized pre-filled syringes (APFS) corresponding to 10mg, 30 mg and 100 mg will be administered at the study centre by a subcutaneous (SC) injection every 4 weeks for the first 3 doses and then every 8 weeks thereafter with the last dose of IP administered at week 48.

Comparator, dosage and mode of administration

Matching placebo solution for injection in an accessorized pre-filled syringes (APFS) will be administered at study centre by a subcutaneous (SC) injection in the same schedule as investigational product. Each study subject will receive two syringes with a fill volume of 1 ml and 0.5 ml respectively to achieve blinding in a double dummy fashion.

Duration of treatment

Following the initial enrolment at Week -4 the subject will enter a 3-week screening/run-in period which is followed by a 56-week double-blind, randomised treatment period, with the last dose of benralizumab/placebo administered at week 48 and end the of treatment (EOT) visit at week 56. Visit 1 (enrolment visit) and Visit 2 (start of screening/run-in) can occur on the same day if there are no restrictions to medications for spirometry. Visit 2 may take place as soon as the medication restrictions prior to spirometry are met, and should occur no later than one week after Visit 1.

Final follow-up visit will be conducted at week 60. For discontinuation procedures refer to section 3.6.1.

The total planned study duration for each subject is approximately 64 weeks.

Statistical methods

The primary efficacy variable is the annual COPD exacerbation rate and the two key secondary endpoints are change from baseline in pre-dose/pre-bronchodilator FEV_1 at Week 56 and also change from baseline in St. George's Respiratory Questionnaire (SGRQ) at Week 56. The exacerbation rate in each of the three benralizumab dose groups will be compared to the exacerbation rate in the placebo group using a negative binomial model including covariates of treatment group, eosinophil cohort (220-299/μL or ≥300/μL), country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and the number of exacerbations in the year before the study. The logarithm of the follow-up time will be used as an offset variable in the model. Change from baseline in pre-dose/pre-bronchodilator FEV_1 at Week 56 will be compared between each of the three benralizumab dose groups and placebo using a repeated measures analysis. Treatment group will be fitted as the explanatory variable. Eosinophil cohort (220-299/μL or ≥300/μL), country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and baseline pre-bronchodilator FEV_1 will be fitted as covariates. Visit will be fitted as a categorical variable.

Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 56 will be analyzed using a similar model as the model for change from baseline in pre-dose/pre-bronchodilator FEV_1.

The primary endpoint and the two key secondary endpoints will be analyzed primarily using the subjects with baseline blood eosinophil counts ≥220/μL in the full analysis set. The full analysis set includes all randomised subjects who received any dose of investigational product. In addition, the exacerbation rate and the two key secondary endpoints will also be summarized in subjects with baseline blood eosinophil counts <220/μL, <150/μL, 150-219/μL, 220-299/μL, 300-449/μL, and ≥450/μL separately for descriptive purpose only.

Multiplicity will be adjusted for the primary endpoint and the two key secondary endpoints on the analysis of subjects with baseline blood eosinophils ≥220/μL for the comparisons of 30mg vs. placebo and 100mg vs. placebo according to a gatekeeping procedure (see section 8.5). Multiplicity will also be adjusted for the primary endpoint and the two key secondary endpoints on the analysis of subjects with baseline blood eosinophils ≥220/μL for the comparisons of 10mg vs. placebo according to a serial gatekeeping procedure (see section 8.5).

The study will recruit subjects with blood eosinophil counts ≥220/μL and <220/μL at a ratio of approximately 2:1 and the study is powered for the primary efficacy analysis of the subjects with blood eosinophils ≥220/μL. For the primary endpoint annual COPD exacerbation rate, 348 subjects with baseline blood eosinophil counts ≥220/μL per treatment arm (1392 total) will need to be randomised to achieve 90% power of detecting a 30% reduction in both the

30mg and 100mg benralizumab dose groups versus placebo after multiplicity adjustment. This calculation has assumed two-sided 4% alpha level test, an annual placebo rate of 0.93 events/subject (1.0 events/subject/56 weeks), a negative binomial shape parameter of 0.4, and a dropout rate of 10%. The sample size calculation is based on simulations and has accounted for the power loss from a proposed futility analysis. According to the approximately 2:1 ratio, the study will also enrol 174 subjects/arm (696 total) with baseline blood eosinophil counts <220/μL. An additional 20 subjects/arm will also be recruited to the 220-299/μL cohort to better characterize patients within this cohort. This addition results in 368 subjects/arm in the ≥220/μL cohort (1472 total). A total of 2168 subjects are expected to be randomised in the study. Details of the estimated numbers of recruited subjects/arm in each cohort (<220/μL, 220-299/μL, ≥300/μL) are described in the SAP.

An unblinded futility analysis based on the primary endpoint will be conducted in this study. The futility analysis will be carried out using pre-defined rules by an external Independent Data Monitoring Committee in order to ensure the integrity of the blinded nature of the study. Furthermore, an internal blinded estimate of the overall exacerbation rate and shape parameter will be conducted before the last subject with eosinophil counts ≥220/μL is randomised. The review may result in an adjustment to the sample size.

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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADA	Anti-drug-antibodies
AE	Adverse event (see definition in section 7.1.1)
AECOPD	Acute Exacerbations of COPD
ALP	Alkaline phophatase
ALT	Alanine aminotransferase
APFS	Accessorised pre-filled syringes
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the curve
BAL	Bronchoalveolar lavage
BD	Bronchodilator
BDI/TDI	Baseline/Transitional Dyspnea Index
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CAT	COPD assessment tool
CGIC	Clinician Global Impression of Change
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
C_{trough}	Pre-dose (trough) concentration
CXR	Chest X-ray
D	Day
DAE	Discontinuation of Investigational Product due to Adverse Event
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid

Abbreviation or special term	Explanation
DUS	Disease under Study
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECP	Eosinophil Cationic Protein
ED90	Benralizumab dose corresponding to 90% of maximum efficacy
eCRF	Electronic case report form
EOT	End of Treatment
EQ-5D	European Quality of Life-5 Dimensions
ePRO	Electronic patient reported outcome
ERS	European Respiratory Society
E-RS	Exacerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms
EXACT-PRO	Exacerbations of Chronic Pulmonary Disease Tool – Patient-reported Outcome
FEV_1	Forced expiratory volume in one second
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
FWER	Family-wise error rate
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Pulmonary Disease
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
GMP	Good Manufacturing Practice
KHK	Kyowa Hakko Kirin Group
HCG	Human chorionic gonadotropin
HCP	Healthcare practitioner
HIV-1/2	Human immunodeficiency virus-1/2
HPF	High power field
IAC	Independent Adjudication Committee
IATA	International Air transport Association
IC	Inspiratory Capacity
ICF	Informed consent form

Abbreviation or special term	Explanation
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
IDMC	Independent data monitoring committee
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-5Rα	Interleukin-5 receptor alpha subunit
IM	Intramuscular
IND	Investigation New Drug (application)
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LSLV	Last Subject Last Visit
LTOT	Long term oxygen therapy
mAb	Monoclonal antibody
MCV	Mean corpuscular volume
mMRC	Modified Medical Research Council
nAb	Neutralizing antibodies
NOAEL	No-observed-adverse-effect level
O_2	Oxygen
OAE	Other Significant Adverse Event
PGIC	Patient Global Impression of Change
PI	Principal Investigator

Abbreviation or special term	Explanation
PK	Pharmacokinetics
PN	Predicted Normal
PRN	Pro Re Nata (as needed)
PRO	Patient reported Outcome
Q4W	Every 4 weeks
Q8W	Every 8 weeks
Q12W	Every 12 weeks
R	Randomisation
RBC	Red blood cell
SABA	Short acting beta-agonist
SAE	Serious adverse event (see definition in section 7.1.2)
SAMA	Short acting muscarinic antagonists
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SpO$_2$	Oxygen saturation via pulse oximetry
TB	Tuberculosis
TEAEs	Treatment emergent adverse events
TESAES	Treatment emergent serious adverse events
ULN	Upper limit of normal
UNS	Unscheduled
V	Visit
W	Week
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

Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and mortality worldwide. In contrast to other chronic diseases, COPD is increasing in prevalence and is projected to be the third-leading cause of death and disability worldwide by 2020 (Global Initiative for Chronic Obstructive Lung Disease (GOLD 2013)).

Acute exacerbations of COPD (AECOPD) are responsible for a large portion of the economic burden of COPD. An AECOPD is defined as a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD (Rodriquez-Roisin R 2000). In addition to a substantial economic burden, AECOPD is also responsible for much of the morbidity and mortality from COPD. Patients with frequent AECOPD show associated increased inflammation and accelerated decline in lung function as compared to patients with infrequent exacerbations (Donaldson et al 2002).

While airway inflammation in COPD has been traditionally described as being predominately neutrophilic, elevated blood and sputum eosinophils have been reported in a subset of COPD patients (Saha and Brightling 2006; Bafadhel et al 2011). Approximately 30-40% of patients with COPD have elevated levels of eosinophils in the airway as measured by sputum induction or bronchoalveolar lavage (BAL; Brightling et al 2000; Brightling et al 2005; Pizzichini et al 1998; Leigh et al 2006; Saha and Brightling 2006). The prevalence of elevated blood eosinophils in COPD has been less well characterized; however, blood eosinophils have been reported to be an accurate predictor of >3% sputum eosinophils in COPD (Bafadhel et al 2011).

In some patients with COPD, the response to oral and inhaled corticosteroids may be related to the degree of airway eosinophilic inflammation (Brightling et al 2000; Brightling et al 2005). In several studies, a sputum eosinophilia ≥3% has been demonstrated to be a good predictor of response to steroids in COPD (Pizzichini et al 1998; Leigh et al 2006; Siva et al 2007). Befadhel et al (Bafadhel et al 2009) showed that a management strategy that aims to minimize eosinophilic airway inflammation and symptoms is associated with a significant reduction in the frequency of COPD exacerbations requiring hospital admission. Evidence also indicates that COPD patients with increased sputum eosinophil counts had significant improvements in forced expiratory volume in 1 second (FEV_1) and quality of life-scores that were associated with decreased sputum eosinophil counts, eosinophil cationic protein (ECP), and IL-5 levels (Pizzichini et al 1998;Bafadhel et al 2009). There are some reports indicating that steroids were not able to reduce eosinophilic airway inflammation in COPD (Brightling et al 2005). Furthermore, a recent report suggested that patients with elevated eosinophils in blood may have an inappropriate response to systemic steroids with worsening in several biomarkers (Bafadhel et al 2011)

These data suggest that therapies specifically targeting eosinophils in COPD patients with elevated eosinophils in the blood or airways may have beneficial effects and that not all patients with eosinophilic inflammation associated with COPD will respond adequately to steroids, particularly inhaled steroids. Treatment options are limited in severe exacerbations of COPD and by depleting eosinophils in the periphery and sputum; benralizumab may be an alternative treatment option for this high unmet need in COPD associated with elevated blood and/or sputum eosinophils.

Interleukin-5 is a cytokine secreted predominantly by T-lymphocytes, mast cells, and eosinophils and is involved in regulating the differentiation, proliferation, and activation of eosinophils via the human IL-5 receptor (IL-5R; Kouro and Takatsu 2009). The human IL-5R is a heterodimer consisting of an α-chain and a β-chain. Monomeric IL-5Rα is a low affinity receptor, while dimerization of IL-5Rα with the β-chain produces a high affinity receptor (Tavernier et al 1991). In the absence of IL-5 interaction with the α-chain, binding to the β chain alone by the ligand does not occur (Takatsu 1995). Expression of the IL-5Rα chain is restricted largely to eosinophils, basophils, and some mast cells in humans (Toba et al 1999; Dahl et al 2004). The α-chain exclusively binds IL-5 and the intracellular portion of IL-5Rα is associated with Janus kinase 2, a protein tyrosine-kinase essential in IL-5 signal transduction (Ogata et al 1998; Takaki et al 1994). Interleukin-5 is the key growth/survival factor for eosinophils; therefore, suppression of eosinophils by targeting IL-5Rα should have a beneficial effect in COPD.

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. Benralizumab is being developed for the treatment of both chronic obstructive pulmonary disease (COPD) and persistent (i.e., nonseasonal) asthma associated with elevated eosinophils. The IND for benralizumab was originally submitted by BioWa, Inc, a member of the Kyowa Hakko Kirin (KHK) Group, on 29 Jun2006. MedImmune accepted transfer of IND 100237 on 07Mar2007 and assumed responsibility for the clinical development program outside of specific Asian countries. The monoclonal antibody (mAb) is also being developed by KHK in Asia under the product name "KHK4563" in parallel with our development program for the asthma indication.

1.2   Rationale for study design, doses and control groups

The final results of study MI-CP196 support conducting this Phase 3 study in patients with COPD with severe and very severe disease, treated with double (ICS/LABA, LABA/LAMA) and triple therapy (ICS/LABA/LAMA), who have elevated peripheral eosinophils. The greatest improvements in the annual exacerbation rate were observed in patients with increasing blood eosinophils (specifically ≥200 and ≥300/μL) based on a pre-specified subgroup analysis (predose FEV_1 and health-related quality of life as measured by SGRQ-C). In patients with low eosinophil counts (<300/μL), the exacerbation signal was not commensurate with what was observed in the high eosinophil group, and the exacerbation rate was not favourable for benralizumab, although the changes in FEV_1 and SGRQ-C were directionally similar to the high eosinophil group.

The clinical development program for benralizumab is designed to evaluate benralizumab's ability to reduce the COPD exacerbation rate in patients with moderate to very severe COPD.

The proposed Phase 3 subject populations are patients with moderate to very severe COPD, as evidenced by a post-bronchodilator FEV_1 >20% and ≤65% of predicted normal (GOLD 2013).

It was not considered appropriate to include patients with mild to moderate disease without exacerbations, or those being treated with single therapy. This is similar to the population explored in recent trials such as SPARK (Wedzicha et al 2013), which essentially evaluated the effect of triple versus double therapy in a severe to very severe patient population. Patients on monotherapy have several therapeutic options available before a biologic becomes part of their therapeutic options.

The proposed benralizumab Phase 3 study will evaluate the efficacy and safety of benralizumab in patients who are uncontrolled despite standard of care therapies (double such as ICS/LABA, LABA/LAMA or triple such as ICS/LABA/LAMA) as evidenced by 2 or more moderate exacerbations or 1 or more severe exacerbation(s) in the previous year. Moderate exacerbations are defined as those requiring treatment with systemic steroids and/or antibiotics. Severe exacerbations are defined as those requiring a COPD related hospitalization or result in death. Hospitalization will be further defined as an inpatient admission ≥24 hours in the hospital, in an observation area, the emergency department or other equivalent healthcare facility depending on the country and healthcare system.

Subjects in this Phase 3 study will be stratified by country and blood eosinophil levels (≥300/µL or <300/µL) with a blood eosinophils boundary of ≥220/µL used for the primary and secondary efficacy analyses. Randomization will be capped at the study level for the baseline eosinophil cohorts (<220/µL, 220-299/µL, ≥300/µL) in order to keep predefined cohort sample size and approximately 2:1 ratio of subjects above and below the boundary of 220/µL.

Based on the efficacy observed in CP196 and recent data in the literature (Pascoe S et al 2015), the primary endpoint will be powered and conducted in subjects with blood eosinophil count ≥220/µL. Subjects with lower blood eosinophils levels (<220/µL) will be included to assess the benefit:risk relationship of benralizumab in COPD patients with a broad range of blood eosinophil levels. Descriptive statistics will be used to assess efficacy in COPD subjects across a broad spectrum of eosinophil levels as detailed in the SAP in order to better identify patients who are likely to benefit from benralizumab and also to evaluate inflection points for efficacy and safety to better define which patients need to be treated with this compound.

Three dose levels 10, 30 and 100 mg Q8W benralizumab will be evaluated in this Phase 3 study in COPD subjects, based on PK and eosinophil modelling, observed incidence of ADA, clinical efficacy, and safety.

Since only one dose level was investigated in Study MI-CP196, the dose-efficacy relationship of benralizumab in COPD has not been fully evaluated. Simulations indicate that the Q12W regimen is associated with a broader distribution of peripheral blood eosinophil counts. This

implies inadequate depletion of eosinophils in many COPD patients following Q12W treatment. Considering that a potentially higher ADA incidence may be associated with infrequent dosing, low and variable PK level, and likely loss of treatment effect in a small subset of ADA-positive subjects, there is no rationale to pursue the Q12W regimen for Phase 3 in COPD. On the other hand, given the low ADA incidence in COPD subjects, in terms of peripheral blood eosinophil depletion, the Q4W dosing does not appear to convey much apparent improvement over the Q8W regimen.

While a 2 mg dose is expected to reduce the blood eosinophil count by half, it is likely associated with a higher risk of immunogenicity response and inadequate eosinophil depletion in tissues. In asthma subjects (Study MI-CP220), no apparent therapeutic efficacy on exacerbation reduction was observed at this dose level. Doses ≤10 mg are likely suboptimal in terms of tissue eosinophil depletion and therapeutic effect (drug level in lung will be much lower than in blood).

For the asthma program, a dose regimen of 30 mg Q8W (ED90 of AER, ACQ, and FEV_1) was selected for Phase 3 studies. This dose is anticipated to maintain steady-state PK exposure in the majority of subjects to potentially reduce the impact of PK variability (body weight, ADA, delayed visits) on therapeutic effect of benralizumab. This was supported through eosinophil and efficacy modelling and simulations. Since the PK of benralizumab and eosinophil response were similar in asthma and COPD subjects, the 30 mg Q8W dose is expected to maintain substantial depletion of blood eosinophils in COPD as well. A 30 mg dose is also convenient for drug product and injection device development, as the same dose will be used for both the asthma and COPD indications. The 100 mg Q8W top dose investigated in Studies MI-CP196 and MI-CP220, and a NOAEL Q2W dose of 30 mg/kg in nonhuman primates provided wide safety margin coverage.

1.3   Benefit/risk and ethical assessment

COPD is a progressive disease which is characterized by exacerbations and health related quality of life loss (GOLD 2013). Despite being adequately treated with double and triple therapy, many patients continue to have COPD exacerbations (Wedzicha et al 2013). Benralizumab is aimed at decreasing the number of exacerbations in patients with moderate to very severe COPD who continue to have exacerbations while on standard double or triple therapy.

In a previous study patients who had an eosinophil count ≥300 appeared to have the greatest benefit from the drug and remained the main target of the study. The exacerbation rate reduction was not evident in the <300 eosinophil group although the sample size was small. In order to better identify the eosinophil threshold for predicted response to Benralizumab, and based on recent data in the literature (Pascoe S et al 2015) to support a boundary of 220/μL for the primary analysis, additional patients will be recruited to a ≥220/μL in addition to the ≥300/μL blood eosinophil cohort in this study. This will result in including patients above and below the 220 eosinophil cutoff in an approximately 2:1 ratio, allowing for exploration of the benefit risk profile in the broader population.

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).

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 COPD.

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

1.4 Overall Study Design

This is a randomised, double-blind, double dummy, placebo-controlled, parallel group, multicentre, phase III study to evaluate the efficacy and safety of benralizumab (MEDI-563), 10mg, 30mg and 100mg dose administered by subcutaneous (SC) injection every 4 weeks for the first 3 doses and then every 8 weeks thereafter with the last dose of IP administered at week 48 and last treatment evaluation performed at week 56, in subjects with moderate to very severe COPD receiving standard maintenance therapy (inhaled corticosteroid/long-acting β2 agonist (ICS/LABA), long-acting β2 agonist /long acting muscarinic antagonist (LABA/LAMA) or ICS/LABA/LAMA) with a history of COPD exacerbation(s) in the year prior to enrolment (Visit 1).

The study will recruit approximately 2168 subjects randomised 1:1:1:1 to the treatment arms, stratified by country and blood eosinophil count (≥300/μL and <300/μL strata).The subject recruitment will be capped at the study level for the cohorts with baseline eosinophil counts <220/μL, 220-299/μL, and ≥300/μL in order to keep predefined cohort sample size and approximately 2:1 ratio of subjects above and below the boundary of 220/μL. Details of the estimated numbers of recruited subjects/arm in each cohort (<220/μL, 220-299/μL, ≥300/μL) are described in the SAP.

The investigational product (IP) will be administered at the study centre every 4 weeks for the first 3 doses, and then every 8 weeks thereafter, the last dose will be given at week 48 and the last treatment evaluation will be performed at week 56.

After the initial enrolment period and confirmation of the entry criteria, subjects will proceed to the screening/run-in period for 3 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Subjects who meet the eligibility criteria will be randomised to a 56-

week treatment period, with last dose of benralizumab/placebo administered at week 48 and the end of treatment (EOT) visit at week 56. Subjects will be maintained on their currently prescribed maintenance therapy (ICS/LABA, LABA/LAMA or ICS/LABA/LAMA), from enrolment throughout the run-in and treatment period.

Final follow-up visit will be conducted at Week 60.

For discontinuation procedures refer to Section 3.6.1.

Figure 1   **Study Flow Chart**

Visit 1	Run-in from V2 until V4		Double blind randomised treatment period		EOT	Final FU
	Visit 2	Visit 3	Visit 4 (w0)	Visit 4-Visit 7	Visit 8-Visit 18	Visit19	Visit 20
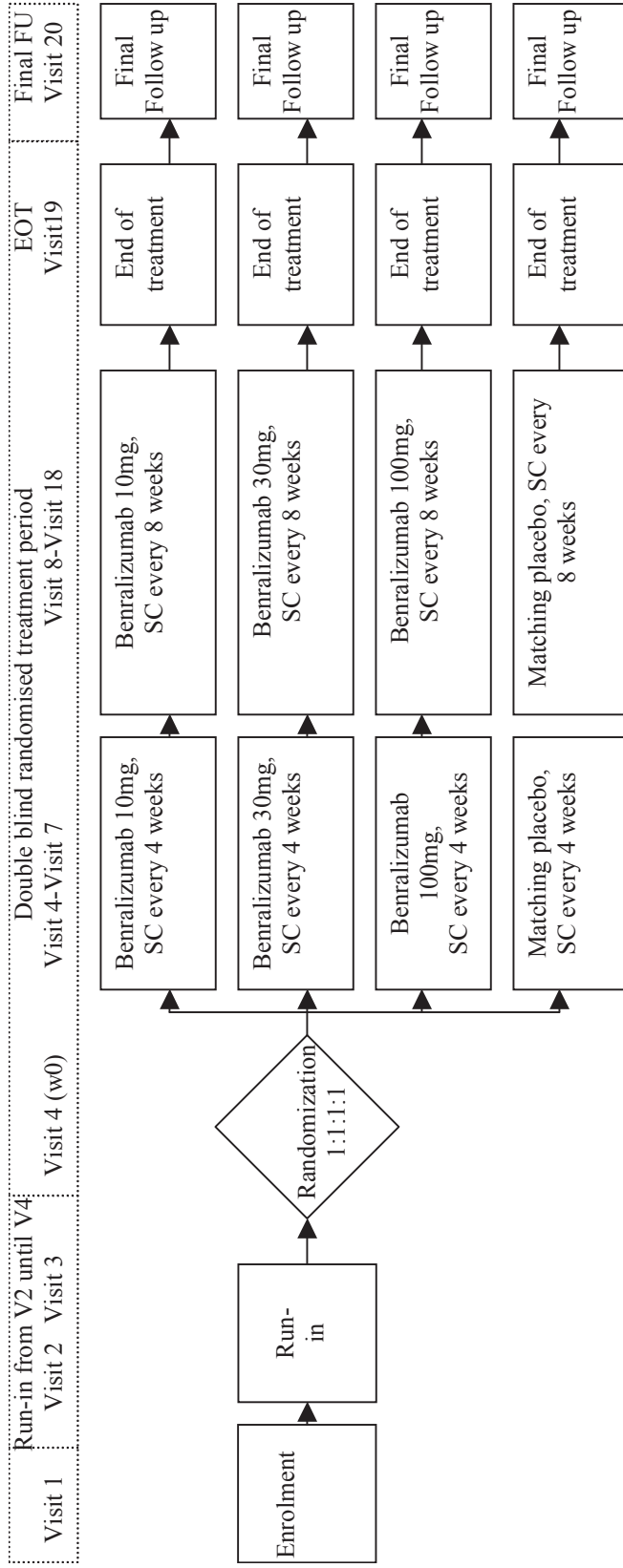
2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To evaluate the effect of three doses of benralizumab on COPD exacerbations in subjects with moderate to very severe COPD	Annual COPD exacerbation rate, where a COPD exacerbation is defined by symptomatic worsening of COPD requiring: • Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids; and/or • Use of antibiotics; and/or • An inpatient hospitalization or death due to COPD

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To evaluate the effect of three doses of benralizumab on health status/health-related quality of life	• SGRQ* • CAT
To evaluate the effect of three doses of benralizumab on pulmonary function	Pre-dose/pre-bronchodilator FEV_1* at the study centre
To evaluate the effect of three doses of benralizumab on respiratory symptoms	• BDI/TDI • E-RS
To evaluate the effect of three doses of benralizumab on rescue medication use	Total rescue medication use (average puffs/day)
To evaluate the effect of three doses of benralizumab on nocturnal awakenings	Number of nights with awakening due to COPD

Secondary Objective:	Outcome Measure:
To evaluate the effect of three doses of benralizumab on the severity, frequency and duration of EXACT-PRO defined events	EXACT-PRO
To evaluate the effect of three doses of benralizumab on other parameters associated with COPD exacerbations	Time to first COPD exacerbation and proportion of subjects with ≥1 COPD exacerbation
To evaluate the effect of three doses of benralizumab on COPD exacerbations involving emergency room visits and hospitalizations	Annual rate of COPD exacerbations that are associated with an emergency room visit or a hospitalization
To evaluate the effect of three doses of benralizumab on health care resource utilization due to COPD	Annual rate of hospitalizations due to COPD; annual rate of hospitalizations and emergency department visits combined due to COPD; annual rate of unscheduled outpatient visits including unscheduled visits to study centres due to COPD; and annual rate of unscheduled healthcare encounters due to COPD
To evaluate the pharmacokinetics and immunogenicity of three doses of benralizumab	• PK parameters • Anti-drug antibodies (ADA)

* Key secondary efficacy endpoints

2.3 Safety objective

Safety Objective:	Outcome Measure:
To evaluate the safety and tolerability of three doses of benralizumab	• AE/SAE • Laboratory variables • 12 lead ECG • Physical Examination • Vital Signs

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measure:
To evaluate the effect of three doses of benralizumab on general health status	EQ-5D-5L
To evaluate the impact of three doses of benralizumab on blood eosinophil levels	Blood eosinophils
To evaluate the effect of three doses of benralizumab on blood biomarkers	Serum biomarkers
To evaluate the effect of three doses of benralizumab on patient and physician global assessments	PGIC and CGIC
To understand the dose response relationship across a broad range of doses	Primary and key secondary endpoints across 3 benralizumab dose levels (10mg, 30mg, and 100mg).
To evaluate the effect of three doses of benralizumab on all cause and respiratory related mortality	Mortality rate

The exploratory analysis will be reported separately.

3. SUBJECT SELECTION CRITERIA, ENROLMENT AND WITHDRAWAL CRITERIA

Each subject enrolled 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 subjects should fulfil the following criteria:

1.   Provision of informed consent prior to any study specific procedures.

2.   Female or male subjects aged 40-85 years inclusive at the time of enrolment (Visit 1).

3.   History of moderate to very severe COPD with a post-bronchodilator $FEV_1/FVC<0.70$ and a post-bronchodilator $FEV_1>20\%$ and $\leq65\%$ of predicted normal value at screening (central spirometry will be used for this criteria assessment).

4.   History of 2 or more moderate COPD exacerbations that required treatment with systemic corticosteroids and/or antibiotics, or 1 or more severe COPD exacerbation(s) that required hospitalization (defined as an inpatient admission ≥24 hours in the hospital, in an observation area, the emergency department or other equivalent healthcare facility depending on the country and healthcare system) within 2 to 52 weeks prior to enrolment. Prior use of antibiotics alone does not qualify as a moderate exacerbation unless the antibiotic was specifically prescribed for the treatment of worsening COPD symptoms.

5.   mMRC score ≥1 at Visit 1

6.   Subjects should have evidence of having been treated with double (ICS/LABA or LABA/LAMA) or triple (ICS/LABA/LAMA) therapy for COPD throughout the year prior to enrolment (Visit 1). It is acceptable for subjects to have stepped up or stepped down during that period of time (from double to triple therapy and vice versa), but they have to be consistently treated with locally approved COPD medications and on approved doses for at least 2 weeks prior to enrolment (Visit 1). Subjects currently receiving background therapy that is not approved for COPD are not eligible for the study

7.   Current smoker or ex-smoker with a tobacco history of ≥10 pack-years (1 pack year = 20 cigarettes smoked per day for 1 year).

8.   Women of childbearing potential (WOCBP) must use a highly effective form of birth control (confirmed by the Investigator). Highly effective forms of birth control

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

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

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

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

9. Male subjects who are sexually active must be surgically sterile at least one year prior to Visit 1 or must 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. Men with a partner or partners who is (are) not of childbearing potential are exempt of these requirements.

10. Ability to read, write and use electronic devices.

Additional criteria to be checked prior to randomisation:

11. Blood eosinophils due to a subject's stratification and cap for blood eosinophil levels. When any eosinophil cohort (<220/μL, 220-299/μL, or ≥300/μL) is full, subjects in the completed cohort will not be randomised and will be withdrawn from the study.

12. Compliance with the eDiary defined as completing at least 8 EXACT-PRO/E-RS assessments in the 14 day period prior to Visit 4 (i.e. Study days -15 to -1).

13. At least 70% compliance with the subject's maintenance therapy (defined as taking all maintenance medication as scheduled for the day) during the run-in period (from Visit 2 to Visit 4) based on the eDiary.

3.2 Exclusion criteria

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

1. Clinically important pulmonary disease other than COPD (e.g. active lung infection, clinically significant bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency and primary ciliary dyskinesia) or another diagnosed pulmonary or systemic disease that is associated with elevated peripheral eosinophil counts (e.g. allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome) and/ or radiological findings suggestive of a respiratory disease other than COPD that is contributing to the subject's respiratory symptoms.

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

   - Affect the safety of the subject throughout the study

   - Influence the findings of the study or their interpretation

   - Impede the subject's ability to complete the entire duration of study

   Subjects who have epilepsy must be on a stable dose of medication for 30 days prior to Visit 4.

3. Unstable ischemic heart disease, arrhythmia, cardiomyopathy, heart failure, renal failure, uncontrolled hypertension as defined by the Investigator, or any other relevant cardiovascular disorder as judged by the Investigator or any ECG abnormality obtained during the screening/run-in period that in Investigator's judgement may put the patient at risk or negatively affect the outcome of the study.

4. Treatment with systemic corticosteroids and/or antibiotics, and/or hospitalization for a COPD exacerbation within 2 weeks prior to enrolment (Visit 1) or during the enrolment and screening/run-in period, based on last dose of steroids or last date of hospitalization whatever occurred later.

5. Acute upper or lower respiratory infection within 2 weeks prior to enrolment (Visit 1) or during the enrolment and screening/run-in period.

6. Pneumonia within 8 weeks prior to enrolment (Visit 1), based on the last day of antibiotic treatment or hospitalization date, whatever occurred later or during the enrolment and screening/run-in period.

30 (111)

7.   Pregnant, breastfeeding, or lactating women.

8.   Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥1.5 times the upper limit of normal (ULN) confirmed by repeated testing during screening period

9.   Risk factors for pneumonia (including, but not limited to: immunosuppression, neurological disorder with increased risk of aspiration).

10.   Known history of allergy or reaction to any component of the investigational product formulation.

11.   History of anaphylaxis to any other biologic therapy.

12.   Donation of blood, plasma or platelets within the past 90 days prior to Visit 1.

13.   Long term oxygen therapy (LTOT) with signs and/or symptoms of cor pulmonale and/or right ventricular failure. Subjects receiving long term treatment with oxygen >4.0 liters/minute (L/min). While breathing supplemental oxygen, subjects should demonstrate an oxyhemoglobin saturation ≥89%. In order to be admitted to the trial subjects on LTOT have to be ambulatory and be able to attend clinic visits.

14.   Use of any non-invasive positive pressure ventilation device (NIPPV). Note: Subjects using continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) for Sleep Apnea Syndrome are allowed in the study.

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

16.   Fever >37.8°C (100°F) measured using the tympanic temperature (or equivalent oral/rectal/axillary temperature) at Visit 4.

17.   Use of immunosuppressive medication, including rectal corticosteroids and systemic steroids within 2 weeks prior to enrolment (Visit 1) and/or during the enrolment and screening/run-in period.

18.   Receipt blood products within 30 days prior to enrolment (Visit 1).

19.   Receipt of any investigational non-biologic product within 30 days or 5 half-lives prior to Visit 1.

20.   Receipt of any marketed (e.g. omalizumab) or any other monoclonal or polyclonal antibody therapy (e.g. gamma globulin) taken for any reason within 6 months or 5 half-lives prior to Visit 1, whichever is longer.

21.   Receipt of live attenuated vaccines 30 days prior to Visit 4.

22.   Subjects are excluded if they have any of the following:

- A history of known immunodeficiency disorder including a positive test for human immunodeficiency virus, HIV-1 or HIV-2

- Positive hepatitis B surface antigen, or positive 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 enroll

23.   A helminth parasitic infection diagnosed within 24 weeks prior to Visit 1 that has not been treated with, or has failed to respond to standard of care therapy.

24.   History of alcohol or drug abuse within the past year, which may compromise the study data interpretation as judged by Investigator or Study Physician.

25.   Malignancy, current or within the past 5 years, except for adequately treated noninvasive basal cell and squamous cell carcinoma of the skin and cervical carcinoma-in-situ treated with apparent success more than 1 year prior to Visit 1.

26.   Subjects who in the opinion of the investigator or qualified designee have evidence of active tuberculosis (TB). Subjects with a recent (within 2 years) first-time or newly positive purified protein derivative (PPD) test or Quantiferon test need to complete an appropriate course of treatment before being considered for enrolment. Evaluation will be according to the local standard of care and may consist of history and physical examinations, chest x-ray, and/or TB test as determined by local guidelines.

27.   Scheduled in-patient hospitalization or surgical procedure during the course of the study. Elective hospitalisations that cannot be delayed until after the end of the study need to be discussed with AstraZeneca Study Physician.

28.   Subjects participating in, or scheduled for, an intensive (active) COPD rehabilitation program (subjects who are in the maintenance phase of a rehabilitation program are eligible to take part).

29.   Subjects with lung volume reduction surgery within the 6 months prior to Visit 1. Subjects with history of partial or total lung resection (single lobe or segmentectomy is acceptable).

30.   Employees of the clinical study centre or family members (first-degree relatives) of such individuals or anyone involved in the planning and/or conduct of the study.

31.   Asthma as a primary or main diagnosis according to the Global Initiative for Asthma (GINA) guidelines (GINA 2011) or other accepted guidelines. Subjects

with a past medical history of asthma (e.g. childhood or adolescence) may be included.

32.   Treatment with allergy immunotherapy, active or within 90 days prior to Visit 1.

33.   Previous treatment with benralizumab (MEDI-563).

3.3   Subject Enrollment and Randomisation

Procedures for withdrawal of incorrectly enrolled or randomised subjects are described in section 3.4.

Investigator(s) should keep a record of subjects considered for and included in the study on the subject screening log.

The Investigator will:

1.   Obtain signed informed consent from the potential subject before any study specific procedures are performed.

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

3.   Determine subject eligibility.

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

Subjects will be allocated to the four treatment arms in a 1:1:1:1 ratio. The randomisation numbers will be grouped in blocks. The study will recruit approximately 2168 subjects, randomised 1:1:1:1 to the treatment arms, stratified by country and blood eosinophil count ($\geq$300/μL and <300/μL strata). Subject recruitment will be capped at the study level for the cohorts with baseline eosinophil counts <220/μL, 220-299/μL, and $\geq$300/μL in order to keep predefined cohort sample size and approximately 2:1 ratio of subjects above and below the boundary of 220/μL. Details of the estimated numbers of recruited subjects/arm in each cohort (<220/μL, 220-299/μL, $\geq$300/μL) are described in the SAP. It is expected that the <220/μL cohort will fill first based on prevalence. Instructions for screen failing these subjects from the study after a stratum is closed are noted in the protocol (Section 3.7.2).

Specific information concerning the use of the IWRS/IVRS will be provided in a separate manual. If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

3.4 Procedures for handling incorrectly enrolled or randomised subjects

Subjects 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. Subjects 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.

Where a subject 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 subject from treatment. The AstraZeneca Study Physician must ensure all decisions are appropriately documented.

3.5 Concomitant medications, restrictions during and after the study

3.5.1 Concomitant medication

Information about any treatment in the 3 months prior to Visit 1 (and 1 year prior to Visit 1 for background (maintenance) COPD medications) 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 2 and Table 3) and recorded in the eCRF.

The subject's usual pre-study double (ICS/LABA or LABA/LAMA) or triple (ICS/LABA/LAMA) therapy formulation, dose and regimen, and any other additional allowed COPD medications that may have been taken prior to enrolment, should be continued throughout the enrolment, screening/run-in and treatment period as outlined below.

Background (maintenance) medication

All subjects are required to be treated with maintenance double (ICS/LABA or LABA/LAMA) or triple (ICS/LABA/LAMA) therapy for COPD throughout the year prior to enrolment (Visit 1) and have to be consistently treated with locally approved COPD medications on approved doses for at least 2 weeks prior to Visit 1 and during the course of the study (see inclusion criteria 6).

The aim of this study is to establish the treatment effect of benralizumab as add-on therapy. Therefore the background medications should be maintained at the same dose and schedule from Visit 1 until the end of the study.

During the study, background medications that are given once daily, should be administered in the morning to conform with spirometric measurement requirements. Changes to the subject's maintenance therapy are discouraged during the treatment period, unless judged medically necessary by the Investigator; such changes should be discussed with the AstraZeneca Study Physician, the justification for treatment changes should be documented in the source notes along with the rationale for the change and recorded in the eCRF.

Background (maintenance) medication is not regarded as an investigational product, but will be provided by AstraZeneca locally according to local regulations, in order to maintain appropriate oversight and access to these concomitant therapies from enrolment and up to Week 60 unless the patient withdraws informed consent.

Rescue medication

SABA (short-acting β2-agonists, e.g. salbutamol, albuterol, terbutaline) will be used as rescue medication during the study in the event of a worsening of COPD symptoms. In the rare cases where a subject has an adverse or allergic reaction to salbutamol/albuterol, levalbuterol can be used. The rescue medication is not regarded as an investigational product, but will be provided by AstraZeneca locally according to local regulations, in order to ensure access for this therapy from enrolment and up to Week 60 unless the patient withdraws informed consent.

Allowed Medications to treat a COPD exacerbation

Medications to treat an exacerbation <u>should not be used for more than 14 days</u>. Recent data have suggested that treatment with systemic steroids for shorter periods of time results in similar outcomes with less systemic steroid exposure. Therefore, it is recommended that subjects are treated with a 5 day course of steroids (Leuppi et al 2013) and no longer than 14 days (see section 3.5.2 and Table 1).

3.5.2 Restrictions

The restrictions that apply during the study are summarized in Table 1.

If at discretion of the Investigator a subject needs treatment with any disallowed medication, "step up" or treatment for an exacerbation for greater than 14 days, the Investigator must contact the AstraZeneca Study Physician to discuss justification for disallowed medication use and/or prolonged steroid treatment.

Table 1   Allowed, restricted and prohibited concomitant medication

Unless specifically indicated, all conditions apply from enrolment and throughout the study duration.

Medication	Allowed/ Restricted/ Prohibited	Details
<u>Background (maintenance) COPD medication</u> **double** (ICS/LABA or LABA/LAMA) or **triple** (ICS/LABA/LAMA)	**Allowed**	Subjects should have evidence of having been treated with double (ICS/LABA or LABA/LAMA) or triple (ICS/LABA/ LAMA) therapy for COPD throughout the year prior to Visit 1 and have to be consistently treated with locally COPD approved medications on approved doses for at least 2 weeks prior to Visit 1 and

		throughout the study.
		ICS in a separate, single device is permitted if all of the following criteria are met: - ICS is approved as part of a fixed dose combination product for COPD; - it is administered at the same dose and schedule as in the fixed dose combination product; - it is not given in combination with a LAMA alone. If an Investigator decides to switch a subject who is on an ICS in a separate single device to a fixed-dose combination device therapy, this should be done at Visit 1 and the ICS component has to remain at the same dose and schedule as used in the 2 weeks prior to Visit 1 (provided dose and regimen are locally approved for COPD). Nebulized budesonide is accepted as part of maintenance therapy if the dosing regimen is equivalent to that of budesonide approved as part of a combination product for COPD (e.g. for budosonide/formoterol combination 320mcg/9mcg BID equivalent dose of nebulized budesonide is 0.5mg BID). Nebulized LABA is accepted as part of maintenence therapy.
ICS in addition to COPD ICS maintenance medication	**Restricted**	Can only be given concomitantly with systemic steroids during hopitalisation/ER COPD exacerbation treatment (additional use of ICS outside of this is not allowed).
Systemic corticosteroids (tablets, suspension or injections)	**Restricted**	Prohibited within 2 weeks prior to Visit 1 and throughout the study. Allowed only to treat a COPD exacerbation and should not be used for more than 14 days. If treatment duration is expected to exceed 14 days the AstraZeneca study physician must be contacted.

SABA (short-acting β2-agonists, e.g., salbutamol, albuterol, terbuataline levalbuterol)	**Allowed** as rescue medication and for treatment of acute COPD exacerbation. **Prohibited** if administered as maintenance medication or in a scheduled dose.	Prophylactic use of SABA in the absence of symptoms is discouraged. However, if deemed necessary by the subject and Investigator (e.g. prior to planned exercise), it can be used, but prophylactic inhalations should not be recorded in the daily eDiary, such use should be documented in the medical notes and recorded in the eCRF.
SABA (nebulized)	**Restricted** as rescue medication. **Prohibited** if administered as maintenance medication or in a scheduled dose from enrolment and throughout the study duration	Routine use for rescue is discouraged unless it is used for managing an acute COPD exacerbation event OR if the Investigator deems access to nebulized SABA as rescue medication is essential for a specific subject. Occasions (# of times used) where SABA was administered via nebulisation will be recorded separately from metered dose inhaler (MDI) inhalations in the eDiary.
SAMA (short acting muscarinic antagonists = short acting anticholinergics; e.g. Ipratropium bromide, MDI or nebulized)	**Allowed** if administered as part of double/triple maintenance therapy in a scheduled dose. **Restricted** as rescue medication and if used as a component of combination products (e.g., combivent)	Subject on maintenance treatment should be on a stable dose, not exceeding 2 puffs q 6-8 hours, and not on a concomitant LAMA (long-acting anti-muscarinic agent, e.g. tiotropium). Taken at regularly scheduled intervals (every 6-8 hours) will be considered equivalent to maintenance treatment with LAMA. Rescue use is not allowed unless used concomitantly with systemic CS for managing an acute COPD exacerbation event. Use on their own, or for step-up or step-down are not allowed. When used for managing an acute COPD exacerbation, should not be used for more than 14 days. If treatment duration is expected to exceed 14 days the AstraZeneca study physician must be contacted.
Antitussives prn	**Allowed**	Allowed if not containing ephedrine and/or opiates and/or other bronchodilators.

Mucolytics	**Allowed**	Allowed if not containing ephedrine.
Dermal topical steroids, nasal steroids, topical ophthalmic and otic corticosteroids	**Allowed**	Use of high potency topical steroids for ≥4 weeks prior to enrolment (V1) and during the study is not allowed.
Antihistamines prn not containing ephedrine or bronchodilators	**Allowed**	
Xanthines	**Restricted**	Allowed in a dose equivalent to theophylline ≤400mg q day. For doses greater than 400 mg, the dose has to be stable and blood levels should be confirmed to be equal to or below 12 mg/dl, within 8 weeks prior to Visit 1 or during screening/run-in period. Blood levels greater than 12 mg/dl should be managed according to local standards of care and the Investigator's judgment and discussed with AZ study physician. It is recommended that additional increments in dose are evaluated with blood levels.
Inhaled disodium cromoglycate or nedocromil sodium	**Restricted**	Can only be given concomitantly with systemic steroids during a COPD exacerbation, use on their own or "step-up" is not allowed.
Leukotriene antagonists and 5-lipoxygenase inhibitors	**Restricted**	Should not be used for more than 14 days. If treatment duration is expected to exceed 14 days the AstraZeneca study physician must be contacted. If leukotriene antagonist is discontinued at Visit 1, approximately 72 hours have to elapse before performing spirometry testing at Visit 2.
Antibiotics	**Restricted**	Antibiotics to treat a COPD exacerbation should not be used for more than 14 days. If treatment duration is expected to exceed 14 days the AstraZeneca study physician must be contacted.

		Antibiotics taken for the prevention of a COPD exacerbation (e.g. macrolides, quinolones) are disallowed.
Omalizumab, denosumab or any other monoclonal or polyclonal antibody therapy (e.g. gamma globulin)	**Prohibited**	Disallowed if taken for any reason within 6 months prior to Visit 1 and during the study.
Allergen immunotherapy	**Prohibited**	Disallowed within 90 days prior to Visit 1 and during the study.
Live attenuated vaccines	**Prohibited**	Disallowed within 30 days prior to randomisation, during the treatment period and for 16 weeks (5 half lives) after the last dose of IP.
Ephedrine-containing medication	**Prohibited**	
Systemic treatment with potent Cytochrome P (CYP) 3A4 inhibitors (e.g., ketoconazole)	**Prohibited**	
Roflumilast (Daxas®, Daliresp®)	**Prohibited**	If Roflumilast is discontinued at Visit 1, approximately 7 days have to elapse before performing spirometry testing at Visit 2.

(a)   COPD medication restrictions on the days of scheduled spirometry visits

Spirometry assessments will be performed at the study centre at scheduled visits (see Table 2 and Table 3). There are restrictions regarding the subject's COPD medications prior to the spirometry assessments.

Screening Visit 2: Subjects will be asked to withhold their usual double (ICS/LABA or LABA/LAMA) or triple (ICS/LABA/LAMA) medications on the morning of the screening pre and post BD spirometry (preferably should be at least 12 hours prior to the assessment/24 hours prior to the assessment for once daily medications) for the eligibility assessment (see section 3.1, inclusion criterion 3). In addition, SABA and SAMA should not be used within 6 hours of this spirometry assessment. The subject's usual COPD medications may be administered following completion of the screening lung function procedures.

Treatment Visits 4-19: Subjects will be asked to withhold their usual double (ICS/LABA or LABA/LAMA) or triple (ICS/LABA/LAMA) medications on the mornings of the scheduled spirometry visits and preferably for at least 12 hours prior to the spirometry assessment/24 hours prior to the assessment for once daily medications). This is especially important prior to scheduled spirometry assessments (see Table 3) in order to maintain the integrity of planned efficacy analyses around lung function improvement. In addition, SABA and SAMA should not be used within 6 hours prior to the spirometry assessments. The subject's usual COPD medications may be administered following completion of the pre-BD spirograms. The subject's usual COPD medications may be administered following completion of the lung volume assessments. The IP will be administered at a scheduled visit after the lung volume and/or spirometry assessments.

If the subject has taken their usual double (ICS/LABA or LABA/LAMA) or triple (ICS/LABA/LAMA) medications on the morning of the scheduled spirometry visit, the Investigator/authorized delegate should remind the subject of the importance of withholding their usual morning maintenance therapy, and reschedule the visit for another day, within the allowed window. If rescheduling is absolutely not feasible for the subject, spirometry may be performed with a notation indicating that the lung volume measurements and/or spirometry were performed after the usual double (ICS/LABA or LABA/LAMA) or triple (ICS/LABA/LAMA) medications administered.

If the subject has taken the rescue SABA within 6 hours of the planned centre visit spirometry they should ideally remain at the centre until such time that the 6 hours withholding time has been reached if it does not exceed the 1.5 hour spirometry window or return on another day, within the visit window. If neither of options is feasible for the subject, spirometry may be performed with a notation indicating that the lung volume measurements and/or spirometry were conducted within 6 hours of SABA use.

(b)   COPD medication restrictions at unscheduled visits

COPD medication restrictions at an unscheduled visit may not be feasible, and may be applied at the discretion of the Investigator. Timing of the double (ICS/LABA or LABA/LAMA) or triple (ICS/LABA/LAMA) medications and rescue SABA use relative to the unscheduled spirometry should be recorded.

(c)   COPD medication restrictions at centre visits with scheduled ECG assessment

The subjects should be instructed not to take their usual double (ICS/LABA or LABA/LAMA) or triple (ICS/LABA/LAMA) medications (i.e. LABA) prior to the scheduled ECG assessment. The use of a SABA should be avoided within 6 hours before the ECG assessments.

Medications do not have to be withheld for the Visit 1 and Visit 3 ECG.

Other restrictions

- Fertile and sexually active subjects or their partners should use highly effective contraceptive methods throughout the study and at least for 16 weeks (5 half-lives) after last administration of the IP. Male subjects should refrain from fathering a child or donating sperm from the time of informed consent and for 16 weeks (5 half-lives) after last dose of IP.

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

3.6 Discontinuation from investigational product

Subjects will be discontinued from investigational product (IP) in the following situations:

1. Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment

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

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

4. Severe non-compliance to study protocol

5. Eligibility requirement found not to be fulfilled

6. Pregnancy

7. Lost to follow-up

8. Development of any study specific criteria for discontinuation:

   - Anaphylactic reaction to the investigational product requiring administration of epinephrine

   - Development of helminth parasitic infestations requiring hospitalization

   - If the time between IP administrations is greater than 10 weeks due to a delay in IP dosing

   - Intensive care unit admission (prolonged intubation and mechanical ventilation) for a COPD-related event

Before a decision to discontinue a subject from IP is instituted, the AstraZeneca Study Physician should be consulted regardless of the reason for discontinuation.

The reason for premature discontinuation of investigational product should be documented in the source documentation and recorded in the eCRF.

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Subjects who prematurely discontinued treatment of the IP should return to the study centre and complete procedures described for the EOT 12 weeks (±7 days) after the last dose of IP, see section 3.6.1.

3.6.1 Procedures for discontinuation of a subject from IP

Subjects who prematurely discontinue treatment should return to the study centre and complete the procedures described for the EOT 12 weeks (±7 days) after the last dose of IP.

It is highly recommended that all study procedures, including any scheduled visits and ePRO completion, are continued till EOT visit, if possible. The subject will bring the ePRO device to the EOT visit.

At EOT visit the subject will be given two options on how to be followed up:

- The subject should be encouraged to return for all regular clinic and phone call visits until he/she completes a total of 56 weeks in the study. At week 56 all the procedures described for Visit 19 are to be conducted

- If the subject cannot comply or does not wish to comply with the option above, he/she will be offered to be followed up on a monthly basis via phone calls while continuing eDiary completion, until the subject completes 56 weeks in the study. No further procedures will be performed. The subject's decision needs to be documented and the specific section in the ICF addendum needs to be signed.

The key elements to be collected are AEs/SAEs, changes in concomitant medications, smoking status and COPD exacerbation information.

The Investigator will be instructed to force data transfer from the ePRO device on the day of EOT visit and then to redispense the device to subject. ePRO alerts will still be in place to notify both the subject and the study center of a potential symptom worsening event (see section 5.1.3.7). The subject will be asked to return the ePRO device to the study centre after the subject completes participation in the study (week 56).

- If the subject refuses the two previous options, he/she will need to sign the specific withdrawal of consent portion of the ICF addendum and return all study materials to the study centre.

AstraZeneca will continue to provide maintenance and rescue medications up to 56 weeks from the time of randomisation (see section 3.5.1) unless the patient withdraws consent. It is the Investigator's responsibility to fully evaluate the patient upon discontinuation or withdrawal to ensure that the patient receives appropriate treatment according to his/her clinical status/ condition.

Figure 2   Premature IP discontinuation

<- - -Treatment period - - - >	12 weeks after IP Last dose	Follow up for discontinued subjects	V19 (week 56)

Last dose of IP

Decision on IP Discontinuation

Scheduled visits and procedures continue

EOT Discontinuation visit

12 weeks after the last dose of IP Procedures described for EOT visit in the Protocol

Option 1: Attend all further scheduled clinic and phone visits (w/o IP)

Option 2: Phone Follow-up calls every 4 weeks and eDiary completion. ICF addendum to be signed.

Visit 19 procedures, study completion

Last Phone FU call, study completion

3.7 Withdrawal from the study

3.7.1 Screen failures

Screening failures are subjects who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These subjects should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (i.e. subject does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised subjects).

3.7.2 Withdrawal due to recruitment completion in a randomisation stratum

When any eosinophil cohort (<220/μL, 220-299/μL, or ≥300/μL) is full, subjects in the completed cohort 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 a development of study specific criteria for discontinuation. As with screen failures, no further study related follow-up of these subjects is required.

3.7.3 Withdrawal of the Informed Consent

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

A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. The subject will return all study related materials to the study centre.

If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced.

3.8 Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent 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.

The collection of the biological samples is an integral part of the study.

- A subject who does not allow for further collection or analysis of biologic samples will need to be discontinued.

- In the case a subject allows for collection and analysis of biological samples but specifically withdraws his/her consent for the retention of samples for exploratory research after the end of the study, the subject does not need to be discontinued and will be allowed to continue participation in the study.

The Principal Investigator or designee:

- Ensures subjects' withdrawal of informed consent for the use of donated samples is notified immediately to AstraZeneca.

- Ensures that biological samples from that subject, if stored at the study centre, are immediately identified, disposed of /destroyed, and the action documented.

- Ensures the local laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study centre.

- Ensures that the subject and AstraZeneca are informed about the sample disposal.

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

3.9 Discontinuation of the study

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 eCRF. 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 subjects' interests.

4. STUDY PLAN AND PROCEDURES

Table 2 **Study Plan – Enrolment, screening/run-in period**

Assessment/Activity	Refer to section	Enrolment	Screening/run-in	
		V1 (w −4)[a]	V2 (w −3)[a]	V3 (w −1)
			Visit window (refer to section 4.1)	
		0-7 days prior to V2	Day −21 (±3 d)	Day −7 (±3d)
Informed consent	10.4	X		
Inclusion/exclusion criteria	3.1/3.2	X	X	X
Medical and COPD history	4.1.1	X[b]		
Concomitant medication	.3.5.1	X	X	X
Adverse events	7.1	X	X	X
Acute exacerbation of COPD	5.1.1	X	X	X
Smoking status	4.1.1/5.2.2	X[b]	X	X
mMRC	5.1.3.3	X[b]		
CAT	5.1.3.4	X[b]		
Site assigns ePRO device and trains subject per the training guidelines	5.1.3		X	
Site to check ePRO compliance at each visit	5.1.3			X
Subject uses ePRO device daily at home to complete the following: • Daily Morning – Nocturnal awakening	5.1.3.5/5.1.3.6		X	X

Assessment/Activity	Refer to section	Enrolment	Screening/run-in	
		V1 (w −4)[a]	V2 (w −3)[a]	V3 (w −1)
		Visit window (refer to section 4.1)		
		0-7 days prior to V2	Day −21 (±3 d)	Day −7 (±3d)
– Rescue medication				
– Major/minor symptoms				
• Daily Evening				
– EXACT-PRO/E-RS				
– Rescue medication				
Maintenance Medication				
Complete physical examination	5.2.1.1	X[b]		
Weight, Height	5.2.3	X[b]		
Vital Signs	5.2.4	X[b]		X
Supplemental oxygen (O_2) status	5.3.7	X[b]		
Oxygen saturation (SpO_2)	5.3.8	X[b]		
Chest x-ray (if applicable)	5.3.9	X[b]		
ECG	5.2.5	X[b]		X
Pre and Post BD spirometry	5.1.2		X	
Clinical chemistry	5.2.6	X		X
Haematology	5.2.6	X		X
Urinalysis	5.2.6	X		X
Serology (hepatitis B,C; HIV-1; HIV-2)	5.3.2	X		
Serum pregnancy test	5.2.7	X		
FSH[c]	5.2.7	X		

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Assessment/Activity	Refer to section	Enrolment	Screening/run-in	
		V1 (w −4)[a]	V2 (w −3)[a]	V3 (w −1)
		Visit window (refer to section 4.1)		
		0-7 days prior to V2	Day −21 (±3 d)	Day −7 (±3d)
TB test (if applicable)	4.1.1	X[b]		
Pneumococcal and annual influenza vaccination, if applicable.	5.3.10	X[d]		

a   Visit 1 and Visit 2 can occur on the same day if there are no restrictions to medications for spirometry. Visit 2 may take place as soon as the medication restrictions prior to spirometry are met (see section 5.1.2), and should occur no later than one week after Visit 1.

b   These V1 procedures can be performed at any time between Visit 1 and Visit 2 inclusive.

c   FSH test done only for female subjects to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 month

d   Pneumococcal and annual influenza vaccination can be done at V1 or at any other visit throughout the study (except for within ±7 days of IP administration) at the discretion of investigator.

Table 3 Study Plan – Randomisation, treatment period and follow-up

Assessment/ Activity	Refer to section	R V4 w0 ±0	V5 phone w0 d6 ±2	V6 w4 ±3	V7 w8 ±3	V8 phone w12 ±7	V9 w16 ±7	V10 phone w20 ±7	V11 w24 ±7	V12 phone w28 ±7	V13 w32 ±7	V14 phone w36 ±7	V15 w40 ±7	V16 phone w44 ±7	V17 w48 ±7	V18 phone w52 ±7	EOT V19 w56 ±7	Final FU V20 w60 ±7	Phone FU[g]	UNS[h]
Visit window (days)[a]																			N/A	N/A
Inclusion/exclusion criteria	3.1/3.2	X																		
Randomisation	4.2	X																		
Concomitant medication	3.5.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	7.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Acute exacerbation of COPD evaluation	5.1.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Smoking status	5.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Healthcare resource utilization	5.1.4	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
CGIC and PGIC	3.5.1						X		X		X						X			
SGRQ	5.1.3.1	X		X			X		X		X		X		X		X			
BDI	5.1.3.2	X																		

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Revised Clinical Study Protocol
Drug Substance Benralizumab (MEDI-563)
Study Code D3251C00004
Edition Number 4.0
Date 06 July 2015

Assessment/ Activity	Refer to section	R		Treatment														EOT	Final FU	Phone FU[g]	UNS[h]
		V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20		
		w0	w0 d6 (phone)	w4	w8	w12 (phone)	w16	w20 (phone)	w24	w28 (phone)	w32	w36 (phone)	w40	w44 (phone)	w48	w52 (phone)	w56	w60	phone	N/A
Visit window (days)[a]		±0	+2	±3	+3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7	N/A	N/A
TDI	5.1.3.2			X	X		X		X		X		X		X		X			
mMRC	5.1.3.3	X																		
CAT	5.1.3.4	X		X	X		X		X		X		X		X		X			
Site to check eDiary compliance at each visit	5.1.3.5	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Subject uses ePRO device daily at home to complete the following: • Daily Morning – Nocturnal awakening – Rescue medication – Major/minor symptoms • Daily Evening – EXACT-PRO/E-RS – Rescue medication – Maintenance Medication • Weekly (7±2 days) – EQ-5D-5L	5.1.3.5/ 5.1.3.6/ 5.1.3.7/ 5.1.3.8/ 5.1.3.9/ 5.1.3.10	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	

Assessment/ Activity	Refer to section	R	Treatment															EOT	Final FU	Phone FU[g]	UNS[h]
		V4	V5 phone	V6	V7	V8 phone	V9	V10 phone	V11	V12 phone	V13	V14 phone	V15	V16 phone	V17	V18 phone	V19	V20	phone	
		w0	w0 d6	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48	w52	w56	w60		
		+0	+2	+3	+3	+7	+7	+7	+7	+7	+7	+7	+7	+7	+7	+7	+7	+7	N/A	N/A
								Visit window (days)[a]													
Complete physical examination	5.2.1.1	X															X			X
Brief physical examination	5.2.1.2			X	X		X		X		X		X		X		X			
Weight	5.2.3	X																		
Vital Signs	5.2.4	X		X	X		X		X		X		X		X		X			X
Supplemental O$_2$ status	5.3.7	X		X	X		X		X		X		X		X		X			
Oxygen saturation (SpO$_2$)	5.3.8	X		X	X		X		X		X		X		X		X			
ECG	5.2.5								X								X			
Pre-BD spirometry	5.1.2	X		X	X		X		X		X		X		X		X			
Clinical chemistry[b]	5.2.6			X	X				X				X		X		X			
Haematology	5.2.6			X	X				X				X				X	X^c		
Urinalysis	5.2.6			X	X				X				X				X			
Urine pregnancy test (dipstick)[d]	5.2.7	X		X	X		X		X		X		X		X		X			
PK	5.3.4	X		X	X		X		X		X		X		X		X	X		

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Assessment/ Activity	Refer to section	R	Treatment																EOT	Final FU	Phone FU[g]	UNS[h]
		V4	V5 phone	V6	V7	V8 phone	V9	V10 phone	V11	V12 phone	V13	V14 phone	V15	V16 phone	V17	V18 phone	V19	V20	phone	
		w0 d6	w0	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48	w52	w56	w60		
											Visit window (days)[a]										
		+0	+2	+3	+3	+7	+7	+7	+7	+7	+7	+7	+7	+7	+7	+7	+7	+7	N/A	N/A
ADA/nAb[e]	5.3.5.2	X			X		X		X		X		X		X		X	X		
Serum for total IgE and IgE FEIA	5.3.3	X							X								X			
Serum/Plasma Biomarkers	5.3.5	X		X			X		X								X			
ImmunoCAP ECP	5.3.5.1	X		X					X								X			
Plasma fibrinogen	5.3.5.1	X		X					X								X			
Administration of IP[f]	6.8	X		X	X		X		X		X		X		X					

a   All visits are to be scheduled from the date of randomisation and not from the date of previous visit. Randomisation visit should occur 21 (±3) days after Visit 2. If there is a need to postpone Randomisation visit, screening/run-in period can be extended by another 7 days as described in section 4.1.2.

b   Detailed schedule for clinical chemistry tests is provided in section 5.2.6.

c   Eosinophil count to be measured only

d   For WOCBP only, urine HCG test to be done at centre at each treatment visit before the IP administration.

e   nAb will be assessed on all ADA positive samples. Samples that are ADA negative will not be tested for nAb.

f   In case of anaphylaxis additional samples will be taken (see section 6.9)

g   Phone follow-up applicable for subjects that discontinue from IP. Every 4 weeks (± 7 days) after the EOT visit up to week 56 as per the study plan.

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

4.1 Enrolment and screening/run-in period

4.1.1 Enrolment (from Visit 1 to Visit 2)

Each potential subject will provide written informed consent prior to any study specific procedures and undergo assessments applicable for the visit (see Table 2).

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

The Visit 1 assessments are primarily concerned with past medical history, past surgical history, comorbidities and confirmation of the COPD disease state, smoking history, the requisite level of severity based on background medications, spirometry measurements and exacerbation history. It is important to record whether the patient meets criteria for chronic bronchitis (chronic cough and mucus production for at least three months in two successive years) and if the patient has historical or current radiographic evidence (chest radiograph or CT scan) of emphysema.

A historical value of blood eosinophils (highest absolute value of eosinophils in the year prior to V1) is an important part of medical history and needs to be recorded in the pertinent CRF module (if available).

A record of a physician-diagnosed COPD, ICS/LABA, LABA/LAMA or ICS/LABA/LAMA use (Section 3.1, criteria 3 and 6) and COPD exacerbation(s) in the previous year (Section 3.1, criterion 4) is suggested source documentation. A subject's verbal history suggestive of COPD symptoms and/or prior COPD exacerbation(s), but without supporting documentation, is not sufficient to satisfy these inclusion criteria.

Examples of acceptable documentation of the COPD disease state and prior COPD exacerbation(s) include clinic visit (primary or specialist HCP), emergency room or hospital records listing COPD as a current problem, plus documentation of at least two moderate or one severe exacerbation during the 12 months prior to Visit 1. A qualifying historical COPD exacerbation is:

- Use of systemic corticosteroids(a single depot injectable dose of corticosteroids is acceptable), and/or

- Use of antibiotics, and/or

- An inpatient hospitalization due to COPD

Current, regular use of ICS/LABA, LABA/LAMA or ICS/LABA/LAMA for at least 2 weeks prior to enrolment should be documented in the source notes. This documentation may be in

the form of a recent, active medication list as per a HCP note, or filled prescriptions based on a pharmacy record.

Following the registration of a subject at the enrolment visit, the screening procedures will be initiated to assess the study eligibility (inclusion/exclusion) criteria (see Table 2). At Visit 1 central laboratory test for absolute blood eosinophils and for safety will be drawn.

If applicable a TB test should be performed according to the local standard of care as determined by local guidelines.

Duration of enrolment period (from Visit 1 to Visit 2) is up to 7 days. Visit 1 and Visit 2 can occur on the same day if there are no restrictions to medications for spirometry (and no washout period is needed). Visit 2 may take place as soon as the medication restrictions prior to spirometry are met (see section 5.1.2) and should occur no later than one week after Visit 1.

 Visit 2 is primarily concerned with evaluating whether lung function meets the study eligibility criteria. Subjects who are unable to produce acceptable post-bronchodilator spirometry data at V2 to evaluate inclusion criteria may be retested at an unscheduled visit.

At Visit 2 a subject is dispensed with an ePRO device (eDiary) (see section 5.1.3).

Enrolment procedures when any of the eosinophil cohorts is closed

As soon as any of the eosinophil cohorts is closed, it is recommended to split enrolment procedures between Visit1 and Visit 2 (as described in Table 2) and to allow sufficient time between Visit 1 and Visit 2 (up to 7 days) to obtain central eosinophil blood count results. The subjects in the completed cohort will be withdrawn from the study (screen failure), no further study related procedures are required for those subjects (see section 3.7.2).

4.1.2   Screening/Run-in (from Visits 2 to Visit 3)

The run-in period should be 3 weeks (±3 days) in duration (from Visit 2 to Visit 4). Visit 3 should occur 2 weeks (±3 days) after Visit 2. The subjects should remain on their current COPD treatment with no changes throughout screening/run-in period. Assessments applicable for the period are listed in Table 2.

If there is a need to postpone Randomisation visit, run-in period can be extended by another 7 days after consultation and in agreement with Study Physician.

Visit 3 (week -1): Safety assessments and other procedures will be performed at this visit as listed in Table 2.

The subject's eligibility should be evaluated at each visit during the screening/run-in period with the relevant documentation entered in the source and eCRF.

4.1.3 Rescreening

Subjects who experience a COPD exacerbation within 2 weeks prior to Visit 1 or during the enrolment and screening/run-in period should be screen failed. They may be re-screened no sooner than 2 weeks after their last dose of systemic steroids.

Subjects with respiratory infections, excluding pneumonia, within 2 weeks prior to Visit 1 or during the enrolment and screening/run-in period, should also be screen failed and may be re-screened but no sooner than 2 weeks after their last dose of antibiotics.

The subjects who experience pneumonia during the enrolment and screening/run-in period should be screen failed. They may be re-screened but no sooner than 12 weeks after the last day of antibiotic treatment or the last date of hospitalisation, whatever occurred later.

Other instances where rescreening is being considered should be discussed with the AZ Study Physician.

Re-screening only allowed once per subject.

One additional re-screening may be allowed for patients who have been screen failed due to eosinophil stratum/ cohort closure; those instances need to be discussed with the AZ Study Physician.

If a subject is re-screened, a new informed consent form is to be signed, and re-screening Visit 1 procedures must be initiated within 3 working days from the date of the new ICF. Re-screened subject keeps an originally assigned enrolment number.

4.2 Randomised treatment period

4.2.1 Randomisation and treatment period

The inclusion/exclusion criteria at the randomisation visit (Visit 4) will be confirmed. Before randomisation the subject's compliance with his/her maintenance medications and ePRO completion must be confirmed.

Subjects confirmed to be eligible will be randomised at Visit 4 in a 1:1:1:1 ratio to receive benralizumab 10 mg, 30 mg or 100 mg or placebo every 4 weeks for the first 3 doses and then every 8 weeks thereafter with the last dose of IP administered at week 48 and last treatment evaluation performed at week 56.

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

Following randomisation, the subject will enter the 56-week double-blind treatment period with the last dose of benralizumab/placebo administered at Visit 17 (week 48).

Subjects will have scheduled clinic visits at 4-week intervals up to Visit 7 and then at 8 week intervals up to Visit 19 to complete protocol-specific assessments and IP administration, as

listed in Table 3. Telephone visits will also occur as per the study plan, listed in Table 3. The restrictions noted in section 3.5 will continue to apply throughout the treatment period. In case of a COPD worsening/exacerbation (see section 5.1.1), subjects should be evaluated at the study centre, when feasible, at an unscheduled visit, or a scheduled visit if the worsening happens to fall within a scheduled visit window.

Subjects will continue to record their COPD symptoms and responses to the questionnaires using the ePRO device throughout the 56-week treatment period (see section 5.1.3 for details).

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

Subjects who prematurely discontinue from IP (see section 3.6) should return to the study centre and complete procedures described for the EOT visit 12 weeks (±7 days) after the last dose of IP.

Subjects will return the ePRO device and all background/rescue medications at the EOT visit.

Subjects will return the ePRO device at week 56.

Subjects who prematurely discontinue from IP should follow the procedures and visit schedule described in section 3.6.

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

4.3   Follow-up period

Subjects who complete Visit 19 (week 56) will return at week 60 for a final follow-up visit.

5.   STUDY ASSESSMENTS AND PROCEDURES

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as (eCRF) specified in the study protocol 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 Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study centre.

5.1   Efficacy assessments

5.1.1   Assessment of COPD exacerbations

For the purpose of the protocol, a COPD exacerbation will be defined as a change in the subject's usual COPD symptoms that lasts 2 or more days, is beyond normal day-to-day

variation, is acute in onset and may warrant a change in regular medication and leads to any of the following:

– Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids and/or

– Use of antibiotics

– An inpatient hospitalization due to COPD (defined as an inpatient admission ≥24 hours in the hospital, in an observation area, the emergency department or other equivalent healthcare facility depending on the country and healthcare system).

– Exacerbations will be considered moderate if they require treatment with systemic steroids and/or antibiotics, and do not result in hospitalization or death. Exacerbations will be considered severe if they result in hospitalization or death.

Symptoms will be assessed by the subject each morning using an ePRO device (eDiary) for the purposes of a symptom worsening alert. The purpose of this alert is to notify both the subject and the study center of a potential symptom worsening event that warrants contact between the subject and the center for further evaluation.

Each morning the subject will complete 3 questions pertaining to the major symptoms of a worsening event (dyspnea, sputum volume, and sputum color). Subject reported worsening of 1 or more of these symptoms will trigger assessment of the minor symptoms of a worsening event (sore throat, cold, fever without other cause, cough, and wheeze). All questions will have a 24 hour recall period. Questions pertaining to the severity of symptoms vs. their usual state will have 3 response options (e.g. How breathless have you been in the last 24 hours? Less breathlessness than usual, Usual level of breathlessness, More breathless than usual) whereas questions related to the presence or absence of a symptom will have a dichotomous response (e.g. Have you had a sore throat in the last 24 hours? No, Yes, I had a sore throat).

If athere is worsening of at least 2 major symptoms or 1 major and 1 minor symptom for 2 consecutive days an alert directed to the subject and site will be generated by ePRO system.

If an event is not associated with ePRO symptom worsening alert as described above (e.g. technical issue, subject self-reports symptom worsening/exacerbation event, the exacerbation is identified during a visit or phone contact, the exacerbation is evaluated and treated at non-study centre, or an acute/severe symptom deterioration which is not captured in the ePRO system occurs), the Investigator should interview the subject and evaluate potential worsening and duration of the following symptoms:

– Shortness of breath

- − Mucus Volume

- − Mucus purulence

- − Cough

- − Wheezing

- − Sore throat

- − Cold symptoms such as a runny nose or nasal congestion

- − Fever

- − Chest Tightness

- − Other findings

The Investigator should record all pertinent findings (symptom worsening) associated with the exacerbation event and their duration in source documents and in the eCRF exacerbation module.

If an exacerbation is not associated with worsening of COPD symptoms or it was not possible to capture the symptoms (e.g. patient intubated upon arrival to the emergency department), the investigator must document the justification for diagnosing and treating the event as an exacerbation and record it in the eCRF.

The start of an exacerbation is defined as the start date of systemic corticosteroids or antibiotic treatment or hospital admission, whichever occurs earlier, and the end date is defined as the last day of systemic corticosteroids or antibiotic treatment or hospital discharge, whichever occurs later.

For the list of allowed medications to treat a COPD exacerbation please refer to section 3.5.1. Based on recent literature it is recommended that treatment with systemic steroids is done for a total of 5 days, but this remains at the discretion of the treating physician. Treatment with systemic steroids should not exceed 14 days unless discussed with Study Physician.

A COPD exacerbation that occurs ≤7 days of the last dose of systemic steroids (oral, IM, IV) or antibiotics or the last day of hospitalisation will be counted as the same exacerbation event.

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

Study centre evaluations for a COPD worsening may occur as a part of an ordinary centre visit, or as an unscheduled visit, if deemed necessary by Investigator. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study centres (e.g. by

the primary care HCP or at an emergency department/hospital) and details entered into the exacerbation module in eCRF in a timely fashion. Changes in concomitant medication due to an exacerbation must be recorded in the appropriate module of the eCRF.

5.1.2 Spirometry (Pre and Post Bronchodilator Assessments at Clinic Visits)

General requirements

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

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

In case spirometry assessment results at Visit 2 and/or Visit 4 are not of acceptable quality, they should be discussed with AstraZeneca Study Physician to decide on patient eligibility and the need for additional assessments.

Important! Subjects should be instructed not to use their ICS/LABA, LABA or LAMA medication within 12 hours (24 hours for once daily medications) of scheduled centre visit spirometry as this will affect the pre/post BD FEV_1 value; they may be taken subsequently, at the centre. For the same reason subjects should not use their rescue SABA medication (albuterol/salbutamol) 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 criteria.

Options for handling subjects who have inadvertently taken their COPD medication within the restricted window are described in section 3.5.2.

Time of day for scheduled centre visit spirometry

Spirometry testing should be done according to the schedule provided in Table 2 and Table 3. It is recommended that spirometry testing will be initiated in the morning between 6:00 AM and 11:00 AM and all post-randomisation spirometry assessments are 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 should be initiated between 6:30 AM and 9:30 AM.

Spirometry technique

Subjects should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Subjects 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 subject seated in an upright position. If this is not comfortable for the subject,

standing is permitted. The same position should be used by the subject 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. The subject from enrolment throughout the study should use mouthpieces of the same dimension and shape.

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 subject to continue the expiration to be fast and forceful throughout the manoeuvre. Ensure that none of the following has occurred: coughing during the first second, glottis closure, leak or obstruction of the mouthpiece (by the tongue).

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

Post-bronchodilator spirometry

Post-BD spirometry will be performed at V2 for all subjects (to evaluate inclusion criterion 3, see section 3.1).

Maximal bronchodilation will be induced using 4 inhalations of albuterol (90 μg metered dose) or salbutamol (100 μg metered dose) with or without a spacer device within 30 minutes ± 15 minutes of the final pre-BD spirometry measurement. Post-BD spirometry will be performed 20-30 minutes later. If a subject cannot tolerate 4 puffs of beta agonist, a lower number of inhalations may be considered at the investigator's clinical judgment.

Order of administration for the COPD maintenance medication and IP relative to the scheduled pre- and post-bronchodilator spirograms

The subject's usual COPD morning maintenance therapy must not be given until after the initial pre-medication, pre/post bronchodilator spirograms are complete for the reasons discussed above. IP dosing should also be withheld until pre-bronchodilator/post bronchodilator spirometry is complete.

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 subjects predicted normal (PN) values and are pre-programmed into your spirometer (Quanjer et al 2012).

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

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

5.1.3 Patient Reported Outcomes

Subjects will complete PRO assessments at the study center on paper and at home using a handheld electronic device (ePRO). PRO assessments must be collected in a systematic way to ensure data integrity. The following best practice guidelines should be followed when collecting PRO data at the site or via an ePRO device:

For PRO instruments administered during site visits

- Administer before other procedures

  - Always administer PRO instruments before other study procedures

- Provide the right environment

  - Provide a quiet and private location to complete the instrument

- No right or wrong answers

  - Remind subjects that there are no right or wrong answers and that we are asking them to complete these questionnaires because we're interested in hearing directly from them on how they feel.

- Help with procedural questions

  - Make sure the subject understands how to complete the instrument. Instrument instructions are usually self-explanatory but staff may answer questions about procedural issues like what it means to "tick a box".

- Avoid bias: do not clarify the meaning of questions or responses

  - Sometimes subjects will ask center staff to clarify the meaning of a question or response. To avoid introducing any bias, politely tell the subject that you cannot clarify items. Remind them that there are no right or wrong answers. Tell them that they should select the response that best answers the question as they understand it.

- No time limits

- Although most instruments require only a few minutes to complete the subject should be given as much time as is needed

- Review for completeness

  - Prompt review of the questionnaire for completeness will minimize missing data and data queries. If an item is left blank ask the subject if they intended to leave the item blank. Provide an opportunity for the subject to answer if they wish.

- Enter PRO data in appropriate modules of eCRF

For PRO instruments captured at home using an ePRO device

- Guidelines similar to paper

  - Many of the same principles apply for ePRO as paper. Remind subjects that there are no right or wrong answers, avoid bias by not clarifying items, remind subjects that they should complete the ePRO questions in a quiet and private location without help from others.

- Train the subject on ePRO device usage

  - Train the subject on how to use the ePRO device using the materials and training provided by the ePRO vendor

  - Provide guidance on whom the subject should call if they have problems

- Monitor compliance

  - Minimizing missing data is a key aspect of study success. Compliance must be checked at each study visit and should be checked more frequently to identify problems early. If compliance drops below 80% a check-in call from the site to ask the subject if they are having difficulties is highly recommended.

  - Recommended background medication compliance during the study is higher than 80%. It is recommended that compliance levels below 70% prompt the site/investigator to evaluate the reasons for low compliance and to provide re-education to the patient in regards to the importance of compliance. It is strongly recommended that when compliance level falls below 50% the site contacts the Study Physician in order to discuss the potential safety implications for the patient and future decisions.

Additional and more specific details concerning PRO instrument administration are provided in subsequent sections where each instrument is described.

5.1.3.1 St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item PRO instrument developed to measure the health status of subjects with airway obstruction 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 health status. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. 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, 2009).

5.1.3.2 Baseline/Transitional Dyspnea Index (BDI/TDI)

The BDI/TDI is an instrument developed to provide a multidimensional measure of dyspnea in relation to activities of daily living (Mahler et al 1984). The Baseline Dyspnea Index (BDI) provides a measure of dyspnea at a single state, the baseline, and the Transitional Dyspnea Index (TDI) evaluates changes in dyspnea from the baseline state. The instrument consists of three components: functional impairment, magnitude of task, and magnitude of effort. For the BDI, each of these three components are rated in five grades from 0 (severe) to 4 (unimpaired), and are summed to form a baseline total score from 0 to 12. For the TDI, changes in dyspnea are rated for each component by seven grades from -3 (major deterioration) to +3 (major improvement), and are added to form a total TDI score from -9 to +9. Positive scores indicate an improvement, and a change from the BDI or a difference between treatments of 1 point has been estimated to constitute the minimum clinically important difference (MCID) (Mahler et al 2005).

The BDI should be captured at Visit 4. The Visit 4 BDI assessment will serve as a baseline and reference for subsequent TDI assessments.

TDI at post-randomization Visits will be completed using the Visit 4 BDI as a baseline reference point.

The BDI/TDI assessments should be completed according to the instructions and before other study procedures. The BDI/TDI is completed by a trained interviewer, who asks the respondent various questions as part of a medical history, and selects a grade (score) using specific criteria for each of the three components. The same interviewer will complete the BDI and the TDI for an individual subject.

5.1.3.3 The Modified Medical Research Council (mMRC) dyspnea scale

The Modified Medical Research Council (mMRC) dyspnea scale uses a simple grading system to assess a subject's level of dyspnea that consists of five statements about perceived breathlessness. It is an interviewer-administered ordinal scale on which subjects provide their

dyspnea according to five grades of increasing severity (scores ranges from 0 (none) to 4 (very severe))

5.1.3.4   COPD Assessment Test (CAT)

The CAT is an 8-item PRO developed to measure the impact of COPD on health status (Jones et al 2009). The instrument uses semantic differential six-point response scales which are defined by contrasting adjectives to capture the impact of COPD. Content includes items related to cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep and energy. A CAT total score is the sum of item responses. Scores range from 0-40 with higher scores indicative of greater COPD impact on health status.

5.1.3.5   Exacerbations of Chronic Pulmonary Disease Tool – Patient-reported Outcome (EXACT-PRO) and EXACT-Respiratory Symptoms (E-RS)

The EXACT-PRO is a 14-item PRO instrument developed to assess the frequency, severity and duration of COPD exacerbations (Jones et al 2011, Leidy et al 2011). The instrument was developed for daily, at home, administration using a handheld electronic device. Respondents are instructed to complete the diary each evening just prior to bedtime and to answer the questions while considering their experiences "today". The daily EXACT-PRO total score has a range of 0-100 with higher scores indicative of greater severity. Total score changes are used to identify the onset and recovery from an EXACT-PRO defined exacerbation event. In identifying event onset and recovery the EXACT-PRO can provide information on event frequency and duration as well as event severity.

The E-RS is an 11-item PRO developed to evaluate the severity of respiratory symptoms of COPD (Sexton et al 2010, Sexton et al 2011). The E-RS is a subset of items from the EXACT-PRO. The E-RS was designed to be captured as part of the daily EXACT-PRO assessment. Summation of E-RS item responses produces a total score ranging from 0 to 40, with higher scores indicating greater severity. In addition to the total score, symptom domain scores can be calculated for breathlessness (5 items; score range: 0–17), cough and sputum (3 items; score range: 0–11) and chest symptoms (3 items; score range: 0–11) by summing the responses of items within a respective domain. As with the total score, higher domain scores indicate greater severity.

5.1.3.6   EQ-5D-5L

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

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

The EQ-5D-5L will be completed weekly (7±2 days) starting from visit 4 (week 0) throughout week 56 (visit 19) using the ePRO device.

5.1.3.7   Major/minor symptom worsening assessment and alert system

Symptoms will be assessed each morning for the purposes of a symptom worsening alert. The purpose of this alert is to notify both the subject and the study center of a potential symptom worsening event that warrants contact between the subject and center for further evaluation.

Each morning the subject will complete 3 questions pertaining to the major symptoms of a worsening event (dyspnea, sputum volume, and sputum color). Subject reported worsening of 1 or more of these symptoms will trigger assessment of the minor symptoms of a worsening event (sore throat, cold, fever without other cause, cough, and wheeze). All questions will have a 24 hour recall period. Questions pertaining to the severity of symptoms vs. their usual state will have 3 response options (e.g. How breathless have you been in the last 24 hours? Less breathlessness than usual, Usual level of breathlessness, More breathless than usual) whereas questions related to the presence or absence of a symptom will have a dichotomous response (e.g. Have you had a sore throat in the last 24 hours? No, Yes, I had a sore throat).

An alert will be triggered if two or more major symptoms (dyspnea, sputum volume, and sputum color) worsen for two consecutive days or if one major symptom and one minor symptom (sore throat, cold, fever without other cause, cough, and wheeze) worsen for at least two consecutive days. When either of these criteria is met the subject will be alerted via the ePRO device to contact the study center as soon as possible for further evaluation. Likewise the study center will be alerted to contact the subject within approximately 24-72 hours if he or she has not yet contacted the center for further evaluation.

5.1.3.8   Rescue Medication Use

 Rescue medication usage including reliever inhaler and nebulizer use will be captured twice daily. Inhaler usage will be reported as the number of puffs in a given period whereas nebulizer use will be reported as the number of times. Rescue medication usage at night will be assessed in the morning and rescue medication used during the day will be assessed in the evening.

5.1.3.9   Nocturnal Awakenings

Subjects will be asked to report the occurrence of nocturnal awakenings due to COPD symptoms each morning using the ePRO device. A single question with yes/no response options will be used.

5.1.3.10   Maintenance Medication Use

Maintenance medication adherence will be assessed each evening via a single yes/no question. The subject will be asked if they took their regularly scheduled inhaler (yes/no) and instructed not to consider instances of rescue inhaler usage when answering this question.

5.1.4 Healthcare Resource Utilization

Broad-based COPD related health care utilization event information will be collected by the Investigator/authorized delegate in accordance with the schedule provided in Table 3 and recorded in the appropriate eCRF module.

At Visit 4 (week 0) COPD related Healthcare Resource Utilization information will be collected with a one year recall period. All the subsequent visits will collect COPD related Healthcare Resource Utilization information with a recall period of 'since last scheduled visit'.

Note: cases of hospitalization also must be reported as an SAE (see section 7.1.2 and 7.1.9).

5.1.5 Clinician Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC)

The Clinician Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC) instruments are used to evaluate overall response to treatment (change from baseline). The assessments are independent of each other. The subject completes the assessment without reference to the clinician's rating and the clinician completes the assessment without reference to the subject's rating. Both assessments use a 7-point rating scale: 1 = Very Much Improved; 2 = Much Improved; 3 = Minimally Improved; 4 = No Change; 5 = Minimally Worse; 6 = Much Worse; and 7 = Very Much Worse.

The investigator (clinician) and the subject will be asked to rate the degree to which overall COPD status may have changed when compared to baseline (i.e. randomization visit/initiation of study drug). The CGIC and PGIC will be completed at the site visits as indicated in Table 3. It is recommended that the same clinician completes the CGIC for an individual subject.

5.2 Safety assessments

5.2.1 Physical examination

Physical examination will be done in accordance with the schedule provided in Table 2 and Table 3. Baseline data will be collected at Visit 1. Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE as described in section 7.1.

5.2.1.1 Complete physical examination

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

5.2.1.2   Brief physical examination

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

5.2.2   Smoking status

Smoking status will be assessed at each visit starting from enrolment (Visit 1) throughout week 56 (Visit 19) by collecting the subject's response to a single yes/no question from study personnel: 'What is your smoking status as of today, do you currently smoke?

5.2.3   Weight and height

The subject's height will be measured at the screening Visit 1 only. Weight will be measured in accordance with the schedule provided in Table 2 and Table 3.

The subject's weight will be recorded in kilograms and height will be recorded in centimetres.

Weight and height measurements will be performed in light clothing and without shoes.

5.2.4   Vital signs

Pre-dose vital signs (pulse, blood pressure, respiration rate and body temperature) will be obtained in accordance with the schedule provided in Table 2 and Table 3. The vital signs will be taken prior to the blood draw, IP administration, and, if possible, the COPD maintenance therapy. Vital signs should also be taken prior to the per protocol bronchodilator administration if applicable for that visit.

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

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

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

5.2.5   ECG

ECG will be performed in accordance with the schedule provided in Table 2 and Table 3. The equipment will be provided by a central vendor, and only this equipment should be used for assessment throughout the subject's participation in the study.

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

The Investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. The ECG printouts will be signed and dated by the investigator and stored at the study centre. The ECG will be transmitted to a central reader.

5.2.6   Laboratory Safety Assessments

The safety laboratory tests will be performed at a central laboratory. For information on methods of collection, assessment, labelling, storage and shipment of samples please refer to the Laboratory Manual. The safety laboratory samples will be collected in accordance with the schedule provided in Table 2 and Table 3.

Haematology and urinalysis will be assessed in line with the schedule provided in Table 2 and Table 3.

Absolute blood eosinophil count required for subject stratification will be assessed by a central laboratory as a part of safety haematology testing at Visit 1 (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 Investigator's/authorized delegate's judgement should be reported as described in section 7.1.3.

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

Table 4   List of Laboratory Safety Tests

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

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

Table 5   Clinical Chemistry Test Schedule

VISIT	V1	V3	V6	V7	V11	V15	V19
Alkaline phosphatase	X	X	X	X	X	X	X
ALT	X	X	X	X	X	X	X
AST	X	X	X	X	X	X	X
BUN	X	X	X	X	X	X	X
Calcium	X	X					
Chloride	X	X					
CO2 (carbon dioxide)	X	X					
Creatinine	X	X	X	X	X	X	X
Gamma-GT	X	X	X	X	X	X	X
Glucose	X	X					

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VISIT	V1	V3	V6	V7	V11	V15	V19
Phosphorus	X	X					
Potassium	X	X					
Sodium	X	X					
Total bilirubin	X	X	X	X	X	X	X
Total cholesterol	X	X					
Uric acid	X	X					

5.2.7 Pregnancy Test

The following tests are applicable to female subjects only and will be conducted in accordance with the schedule provided in Table 2 and Table 3.

- Serum beta-HCG – the test will be performed at the screening Visit 1 only, for WOCBP (analysed at the central laboratory)

- FSH – the test will be performed at Visit 1 only, for female subjects to confirm postmenopausal status in women <50 years who have been amenorrheic for ≥12 months

- Urine HCG – the test will be performed at the study centre for WOCBP at each treatment visit before IP administration using a urine dipstick. A positive urine test result must be confirmed with a serum beta HCG.

5.3 Other Study Assessments

5.3.1 Central Laboratory Eosinophil Testing

Subjects will be stratified by the absolute blood eosinophil count as assessed by a central laboratory (haematology sample taken at Visit 1, see section 5.2.6), and randomization will be capped at the study level for the baseline eosinophil cohorts (<220/µL, 220-299/µL, ≥300/µL) in order to keep predefined cohort sample size and approximately 2:1 ratio of subjects above and below the boundary of 220/µL. Once any of the eosinophil cohorts is filled, subjects allocated to that particular cohort based on the Visit 1 eosinophil count, will be screen failed (see section 3.7.2).

5.3.2 Serology

Blood samples for the hepatitis B surface antigen and hepatitis C antibody will be taken at Visit 1 and the analysis will be performed at the central laboratory.

Blood samples for the HIV-1 and HIV-2 antibodies will also be taken at Visit 1 and as above the analysis will be performed at the central laboratory.

Instructions for sample collection, processing, storage, and shipment will be found in the central laboratory manual.

5.3.3   Total IgE and IgE FEIA

The test will be performed at Visits 4, 11 and 19, see Table 3. The analysis will be performed at the central laboratory.

Instructions for sample collection, processing, storage, and shipment will be found in the central laboratory manual.

5.3.4   Pharmacokinetics

It is important that date and time of PK sample collection and date and time of IP administration is recorded for each subject.

Serum will be collected pre-dose according to the schedule of study procedures, Table 3.

Samples will be collected, labelled, stored and shipped as detailed in the laboratory manual.

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

A summary of PK analysis results will be reported either in the Clinical Study Report (CSR) itself or as an addendum to the CSR.

The PK samples will be retained at AstraZeneca or designee for a maximum of 15 years following Last Patient Last Visit to properly address potential questions from Regulatory Authorities.

5.3.5   Pharmacodynamics

5.3.5.1   Serum Biomarkers

Serum samples will be collected according to the schedule in Table 3 to analyze predictive biomarkers to further evaluate subject populations responsive to benralizumab, and pharmacodynamic biomarkers to further evaluate the pharmacology of benralizumab. These biomarkers will include pharmacodynamic markers of benralizumab, markers of eosinophil and basophil recruitment, activation and survival, as well as biomarkers of inflammation including cytokines, chemokines, acute phase response proteins, ECP, fibrinogen, serum-amyloid A, procalcitonin, IL-8, vitamin D, and other inflammatory mediators.

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

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of any investigation will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

5.3.5.2 Immunogenicity

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

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

The analysis time points will be determined by the cumulative information obtained from the Asthma and COPD programs and will be described in SAP.

Summary of the analysis will be presented in the CSR.

Anti-benralizumab antibodies

The pre-dose serum samples to measure presence of ADA will be collected according to the schedule of study procedures (see Table 3).

The presence or absence of ADA will be determined in the serum samples using validated bioanalytical method. The method will be summarized in the CSR and fully described in the validation report.

Neutralizing antibodies (nAb)

Neutralizing antibodies (nAb) will be assessed on all ADA positive samples. ADA negative samples will not be tested for nAb.

The presence or absence of neutralizing ADA will be determined using a validated bioanalytical method. The method details will be described in a separate bioanalytical report.

5.3.6 Handling of Biological Samples

5.3.6.1 Labelling and Shipment of Biological Samples

The Principal Investigator or designee ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

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

5.3.6.2 Chain of Custody of Biological Samples

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

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

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

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

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

For the process of Withdrawal of Informed Consent for donated biological samples refer to section 3.8.

5.3.7 Supplemental Oxygen (O$_2$)

Oxygen use will be assessed according to the schedule in Table 2 and Table 3.

5.3.8 Oxygen saturation (SpO2)

Pulse oximetry will be used to measure the subject's oxygen saturation according to the schedule in Table 2 and Table 3.

5.3.9 Chest X-ray

A historical (previously done) chest X-ray (posterior/anterior and lateral) or Computed Tomography (CT) dated within 8 weeks prior to enrolment is required to ensure that there are no abnormal radiological findings that would exclude the subject from study participation as per exclusion criterion 1. If a historical (previously done) chest X-ray (or CT) is not available, it should be done at Visit 1, or at any time prior to randomisation.

5.3.10 Pneumococcal and Annual Influenza Vaccination

Subjects should have a pneumococcal vaccination unless contraindicated if they have not had one before. In the event that they have previously received a vaccination, the Investigator must ensure that the subject does not require a booster (generally after 5-6 years according to current guidelines, e.g. CDC guidelines 2010). If a booster is required, it should be given. Subjects should receive an annual influenza vaccination in the autumn or winter period unless the subject has received it prior to study start (CDC guidelines 2013-2014). If the subject has previously received the influenza vaccination within the last 12 months prior to study start, the vaccination should be given at the next autumn or winter period. If a subject has an egg intolerance or refuses to be vaccinated, the vaccination may be omitted. If the Investigator

makes a decision to not vaccinate with either vaccine, the rationale should be clearly specified.

Pneumococcal and/ annual influenza vaccination can be given at V1 or at any other visit throughout the study (except for ±7 days of IP administration) at the discretion of investigator.

6.   MANAGEMENT OF INVESTIGATIONAL PRODUCTS

6.1   Identity of investigational product(s)

All investigational products will be manufactured at Cook Pharmica LLC, 1300 South Patterson Drive, Bloomington, IN, 47403, USA on behalf of MedImmune in accordance with Good Manufacturing Practice (GMP).

Benralizumab and placebo administered in the study will be a clear to opalescent, colourless to yellow solution. Each study subject will receive two injections from two syringes with a fill volume of 1 ml and 0.5 ml respectively to achieve blinding in a double dummy fashion.

Investigational product	Dosage form and strength	Manufacturer
Benralizumab	20mg/mL solution for injection in accessorized pre-filled syringe, 0.5 mL fill volume	Cook Pharmica LLC on behalf of MedImmune
Benralizumab	30mg/mL solution for injection in accessorized pre-filled syringe, 1mL fill volume	Cook Pharmica LLC on behalf of MedImmune
Benralizumab	100mg/mL solution for injection in accessorized pre-filled syringe, 1mL fill volume	Cook Pharmica LLC on behalf of MedImmune
Placebo	Matching placebo solution for injection in accessorized pre-filled syringe, 1mL fill volume	Cook Pharmica LLC on behalf of MedImmune
Placebo	Matching placebo solution for injection in accessorized pre-filled syringe, 0.5 mL fill volume	Cook Pharmica LLC on behalf of MedImmune

6.2   Labelling

Labelling of the Investigational Product will be carried out by AstraZeneca or designee in accordance with Annex 13 and 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 and required by local regulations.

6.3 Storage

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

The IP must be kept in the original outer container and under conditions specified on the label.

In the following cases the centre staff should not use affected IP and should immediately contact AstraZeneca representative for further guidance:

- – Temperature excursion upon receipt or during storage at the study

- – Damaged kit upon receipt

- – Damaged syringe/cartridge

Damaged IP should be documented using the IWRS/IVRS (please refer to IWRS/IVRS manual for further details).

6.4 Accountability

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

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

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

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

About 10 pre-selected sites in US will participate in APFS return program. These sites will collect in total approximately 100 APFSs presumed to have functioned properly during dosing, and then contact study monitor to initiate return process according to applicable guidelines; the users of the devices will be asked to complete questionnaire to evaluate the device performance. The results of the investigation will be reported either in an addendum to CSR, or separately in a scientific report or publication.

6.5 Methods for assigning treatment groups

Randomisation codes will be assigned strictly sequentially in each stratum as subjects become eligible for randomisation.

Subjects 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.

6.6 Methods for ensuring blinding

The study will be conducted in double blind, double dummy fashion. All packaging and labeling will be done in such way as to ensure blinding. The following personnel will have access to the randomisation list:

–   the personnel carrying out the packaging and labelling of IP

–   the personnel generating the randomisation list

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

AstraZeneca staff involved in the study, the subjects, and the investigators involved in the treatment of the subjects 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 accessorized pre-filled syringes.

Maintaining the blind to the subject's blood eosinophil counts

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

*   Per protocol haematology will be run by the central laboratory. Except for the Visit 1 screening eosinophil count, eosinophil and basophil counts will be redacted from the laboratory reports. Because complete knowledge of the remaining cell types could permit deduction of the 'eosinophil+ basophil' compartment, monocyte counts will also be redacted from the reports.

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

*   Handling of laboratory results obtained during the treatment period but ordered outside of the clinical trial. Centre staff who are directly involved in the subject's management should remain blinded to any eosinophil, basophil and monocyte results included as part of an outside lab reports. To help ensure this, each investigational centre will designate an individual (e.g. administrator or another ancillary person) not directly involved in subject management, to receive and blind any eosinophil, basophil and monocyte results prior to the report being handed over to the centre staff involved in subject's management and prior to filing as a source document. Similarly, eosinophil and basophil results must be redacted from all communications with the Sponsor.

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

6.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the Investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product 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 subject have been made and documented.

6.8 IP administration and treatment compliance

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

The IP will be administered subcutaneously at the study centre on treatment visits and within visit windows as specified in Table 3.

IP should be administered after all other visit procedures are completed.

In cases where a treatment visit needs to bere-scheduled, the IP must be administered within 10 weeks of the previous IP dose. If the time between doses is greater than 10 weeks the subject should be discontinued from IP, please refer to section 3.6.1. Minimum interval between IP doses should not be less than 3 weeks.

If the dose for Visit 6 is significantly delayed (>1 week) this is the only time at which the dose can be skipped, the next dosing should be done at Visit 7 as per Study plan (Table 3).

If IP dosing needs to be delayed, all study procedures for that visit should be postponed until the day of dosing. However if any of treatment visit procedures have been already performed, there is no need to repeat them provided IP is administered within the next 7 days.

Before IP administration

Prior to each IP administration:

– Investigator/authorized delegate will assess the injection site as per standards of medical care

– For WOCBP the urine pregnancy test will be done; IP will be administered only when the result of the test is negative (see section 5.2.7)

IP administration

The IP will be administered by the Investigator/authorized delegate IP is administered subcutaneously. Two injections are required. The two injections will be administered at the same anatomical site with a distance of at least 3 cm between the two injections. It is advised that the site of injection of IP is rotated such that the subject 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 documented in the source at each treatment visit and recorded in the eCRF.

Figure 3   Injection sites and rotation scheme
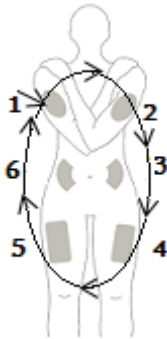
In cases when rotation of the injection site is not favourable for the subject and/or Investigator, the reason for this should be documented in the source as well as injection site at each treatment visit.

The specific details for IP administration are provided in the IP Handling Instruction. The IP administration must be carried out in line with these instructions.

After IP administration

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

Conditions requiring IP administration rescheduling

If a subject presents with a condition that prohibits administration of IP or other events that in the opinion of the Investigator contraindicate dosing, administration of IP will be withheld until the condition resolves, up to a maximum of 10 weeks between IP dosing.

Unscheduled visit procedures may be performed at the discretion of the Investigator.

If there is a delay in the administration of Benralizumab such that it will not be administered within the specified timeframe, the study monitor must be notified immediately. If the time between IP doses is greater than 10 weeks the subject should be discontinued, please refer to section 3.6.

If any of the following occurs, the Investigator should reschedule the visit and investigational product should not be administered until the rescheduled visit:

- The subject has an intercurrent illness, that in the opinion of the Investigator may compromise the safety of the subject in the study (e.g. viral illnesses)

- The subject shows signs of a clinically significant infection during the treatment period. Benralizumab should not be administered to a subject with a clinically significant active infection treated with oral or IV antimicrobials, antivirals, or antifungals until it is confirmed by the investigator that the infection has resolved

- The subject, in the opinion of the Investigator, is experiencing an acute or emerging COPD exacerbation. Benralizumab should not be administered until it is confirmed by the investigator that the exacerbation has resolved

- The subject is febrile (≥38°C; ≥100.4°F) within 72 hours prior to investigational product administration

- The subject has LFTs (ALT and/or AST) of > 3×ULN and concurrent elevated bilirubin > 2×ULN

- Any event that in the opinion of the investigator or the sponsor contraindicates further dosing or could result in complications

6.9 Management of IP related reactions

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

Anaphylaxis will be defined as serious reaction that is rapid in onset and may cause death (Sampson et al 2006). Anaphylaxis typically manifest as one of three clinical scenarios:

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

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; or

3.   Reduced blood pressure after exposure.

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

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

7.   SAFETY REPORTING

7.1   Adverse events

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

7.1.1   Definition of adverse events

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

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

7.1.2   Definitions of serious adverse event

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

- Results in death

- Is immediately life-threatening

- Requires in-patient hospitalisation or prolongation of existing hospitalisation

- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions

- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above

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

7.1.3   Recording of adverse events

Time period for collection of adverse events

All AEs, including SAEs, will be collected from the time the subject signs the informed consent throughout the treatment period up to the final follow-up visit (Visit 20, week 60).

For the patients prematurely discontinued from IP all AEs, including SAEs, will be collected up to Visit 19, week 56.

Follow-up of unresolved adverse events

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

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

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

7.1.4   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 Investigational Product (yes or no)

- Action taken with regard to investigational product

- AE caused subject's withdrawal from study (yes or no)

- Outcome

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

7.1.5 Causality collection

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

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

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

7.1.6 Adverse Events based on signs and symptoms

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

7.1.7 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 to baseline in protocol-mandated laboratory values, 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 investigational product.

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 uses the clinical, rather than the laboratory term (e.g., 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.

7.1.7.1 Adverse events of Pneumonia requiring a confirmed diagnosis

Events of suspected pneumonia should be confirmed by the presence of a new infiltrate on x-ray within approximately 48 hours, as well as at least 2 of the following signs and symptoms: increased cough, increased sputum purulence or production, consistent auscultatory findings, dyspnea or tachypnea, fever, leukocytosis, or hypoxemia.

Events of confirmed diagnoses of pneumonia must be recorded as the adverse event "Pneumonia (confirmed)" in the eCRF.

7.1.8 Drug Induced Liver Injury (DILI)

Cases where a subject shows an AST or ALT ≥3xULN or total bilirubin ≥2xULN may need to be reported as SAEs. Please refer to Appendix D for further instructions in cases of combined increase of aminotransferase and total bilirubin.

7.1.9 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then the Investigators or other centre personnel will inform the appropriate AstraZeneca representatives within one day i.e., 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 the necessary information is provided to the AstraZeneca Patient Safety data entry site within one calendar day of initial receipt for fatal and life threatening events and within five 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 is undertaken immediately. Investigators or other centre personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

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

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

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

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

7.1.10   Reporting of COPD exacerbations

COPD exacerbations should be captured on a specific eCRF module (COPDEX).

COPD exacerbations should not be reported as Adverse Events unless they meet Serious Adverse Event definition (see 7.1.2). In such case, COPD exacerbation should be reported both as an exacerbation and as a SAE.

7.2   Overdose

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module

- An overdose without associated symptoms is only reported on the Overdose eCRF module

If an overdose on an AstraZeneca study drug occurs in the course of the study, then Investigators or other centre personnel inform appropriate AstraZeneca representatives within one day i.e., 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 provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see section 7.1.9. For other overdoses, reporting should be done within 30 days.

7.3   Pregnancy

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

7.3.1   Maternal exposure

If a subject becomes pregnant during the course of the study, the investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product 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 subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then Investigators or other centre personnel inform appropriate AstraZeneca representatives within one day i.e., 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 provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see section 7.1.9 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy (PREGREP) module in the eCRF is used to report the pregnancy and the pregnancy outcome (PREGOUT) module is used to report the outcome of the pregnancy.

7.3.2 Paternal exposure

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

Pregnancy of the subject's partner is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be followed up and documented.

Information on the pregnancy of a male subject's partner must be obtained directly from the subject's partner; the male subject should not be asked to provide this information. Prior to obtaining information related to the pregnancy and outcome of the pregnancy, the Investigator must obtain the subject's partner consent. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 16 weeks (5 half-lives) after the last administration of IP should be followed up and documented.

7.4 Independent Adjudication Committee

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 III trials. The committee will operate in accordance with an Adjudication Committee Charter/Manual of Operations, which will also provide detail on what specific information the committee requires to enable a thorough adjudication.

7.5 Independent Data Monitoring Committee

The Independent Data Monitoring Committee will be responsible for monitoring the safety of the study participants, ensuring that the studies are being conducted with the highest scientific and ethical standards and making appropriate recommendations based on the available data. The IDMC will function independently of all other individuals associated with the conduct of the studies, including the study sponsor AstraZeneca. The committee will operate in accordance with an Independent Data Monitoring Committee Charter (also refer to section

8.5.6). The IDMC will evaluate general safety output including but not limited to wound healing and host defense (infections and infestations). It will also evaluate the output of the independent adjudication committee (major adverse cardiovascular events and malignancies). This will be done in addition to usual pharmacovigilance programs.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified

- Analyses will be performed by AstraZeneca or its representatives

Refer to the SAP for additional details.

8.2 Sample size estimate

The study will recruit subjects with blood eosinophil counts <220/µL, 220-299/µL, and ≥300/µL. The approximately 2:1 ratio between ≥220/µL and <220/µL allows analysis of the primary population for subjects most likely to respond to benralizumab (i.e. ≥220/µL), while still including subjects below this threshold in order to help understand efficacy and safety in this group. The study is powered for the exacerbation rate comparisons of the subjects with blood eosinophils ≥220/µL (primary efficacy analysis).

For the primary endpoint annual COPD exacerbation rate, 348 subjects with baseline blood eosinophil counts ≥220/µL per treatment arm (1392 total) will need to be randomised to achieve 90% power of detecting a 30% reduction in both the 30mg and 100mg benralizumab dose groups versus placebo based on a Hochberg Procedure (Hochberg 1988). This calculation has assumed two-sided 4% alpha level tests, an annual placebo rate of 0.93 events/subject (1.0 events/subject/56 weeks), a negative binomial shape parameter of 0.4, and a dropout rate of 10%. The sample size calculation is based on simulations and has accounted for the power loss from a proposed futility analysis (Section 8.5.6).

As stated previously an approximately 2:1 ratio will be used for subjects with blood eosinophil counts ≥220/µL and <220/µL. Therefore this study will randomise 174 subjects/arm (696 total) with baseline blood eosinophil counts <220/µL. An additional 20 subjects/arm will also be recruited to the 220-299/µL cohort to better characterize patients within this cohort. This addition results in 368 subjects/arm in the ≥220/µL cohort (1472 total). A total of 2168 subjects are expected to be randomised in this study. Details of the estimated numbers of recruited subjects/arm in each cohort (<220/µL, 220-299/µL, ≥300/µL) are described in the SAP.

The sample size necessary to achieve a stated power (90% in our case) in this study is calculated based on the estimate of overall exacerbation rate and shape parameter from the negative binomial model (Section 8.5.1). In order to better estimate the overall exacerbation

rate and shape parameter, we plan to conduct a single blinded sample size re-estimation in both studies D3251C0003 and D3251C0004. Blinded estimates of the overall exacerbation rate as well as the shape parameter from data pooled across placebo and all benralizumab doses (for patients with eosinophil counts ≥220/μL) will be used in the sample size re-estimation and strictly no treatment information will be used in the review. The pooled study summaries will not contain any information that would potentially reveal the treatment assignments (e.g., post-randomization eosinophil levels). The review will be conducted before the last patient with eosinophil counts ≥220/μL is randomized and after the futility analysis (Section 8.5.6). The exacerbation rate and shape parameter will be estimated using the maximum likelihood approach as proposed by Friede and Schmidli 2010. This review may result in an adjustment of sample size. Since this review will be performed in a blinded fashion, no adjustment for the type I error is needed. The blinded data review will be performed by AstraZeneca internal personnel or its designees and the full details of the review will be specified in a blinded data review plan.

8.3 Definitions of analysis sets

8.3.1 All patients analysis set

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

8.3.2 Full analysis set

All subjects randomized and receiving at least 1 dose of investigational product will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. Subjects will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the ITT principle. Subjects who withdraw consent or assent to participate in the study will be included up to the date of their study termination. All efficacy analyses will be analyzed using the full analysis set.

8.3.3 Safety analysis set

All subjects who received at least 1 dose of investigational product will be included in the safety analysis set. Subjects will be classified according to the treatment they actually received. A subject who has on one or several occasions received active treatment will be classified as active. If a subject has received both active doses, then the subject will be classified as the higher active dose. All safety summaries and ADA data will be based on this analysis set.

8.3.4 Pharmacokinetic analysis set

All subjects who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations (e.g., disallowed medication) 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 56-week double-blind treatment period, defined as the period after administration of randomised investigational product at Visit 4 and the EOT at Visit 19, inclusive.

8.4.1.1 Exacerbation rate

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

A COPD exacerbation is defined in section 5.1.1.

In order to calculate the number of exacerbations experienced by a subject during the 56-week treatment period, the following rule will be applied.

The start of an exacerbation is defined as the start date of systemic corticosteroids or antibiotic treatment or hospital admission, whichever occurs earlier, and the end date is defined as the last day of systemic corticosteroids or antibiotic treatment or hospital discharge, whichever occurs later. In the primary analysis, the number of exacerbations observed for a subject during the 56-week double-blind treatment period will be used as response variable.

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

Maximum follow-up time for exacerbations for a subject is approximately 56 weeks; defined as the time from randomisation to the date of Visit 19. For a subject lost to follow-up, this 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 COPD exacerbations experienced by a subject during the 56-week double-blind treatment period will be used as response variable, and the logarithm of the subject's corresponding follow-up time will be used as an offset in the analysis to adjust for subjects having different exposure times during which the events occur.

For the production of summary statistics, the annual exacerbation rate per subject is calculated, and standardized per 56-week period according to the formula described below.

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

For subjects who prematurely discontinue treatment, efforts will be made to continue collecting the exacerbation data until the scheduled Visit 19/ EOT at Week 56 after randomisation (refer to section 3.6.1). In the statistical analysis of exacerbation rate, the data collected up to Visit 19/ EOT at Week 56 will be included for the patients who prematurely

discontinue treatment according to the intent-to-treat principle. For the patients who died during the treatment period the exacerbation data collected up to the date of death will be included in the statistical analysis.

If the cause of death is related to COPD or a COPD exacerbation, the event will also be included in the rate calculation.

8.4.1.2   Proportion of subjects with ≥1 COPD exacerbation during 56 weeks of treatment

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

8.4.1.3   Time to first exacerbation

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

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

The time to first COPD exacerbation for subjects who do not experience an COPD exacerbation during the treatment period will be censored at the date of their last visit for the 56-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up subjects).

8.4.1.4   Forced expiratory volume in 1 second

The change from baseline to each of the post-randomisation visits (post Visit 4) up to and including the end of 56-week double-blind treatment visit (Visit 19) will be used as secondary efficacy variables. The pre-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 COPD exacerbations that are associated with an emergency room visit or a hospitalization

The annual rate of COPD exacerbations that are associated with an emergency room visit or a hospitalization will be a secondary efficacy variable.

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

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

8.4.1.6   Annual rate of healthcare encounters due to COPD

The annual rate of hospitalizations due to COPD, the annual rate of hospitalizations and emergency room visits combined due to COPD, the annual rate of unscheduled outpatient visits including unscheduled visits to study centres due to COPD and all unscheduled healthcare encounters combined due to COPD (hospitalizations, emergency room visits, unscheduled outpatient visits including unscheduled visits to study centres) will be secondary variables.

In the statistical analysis, the number of hospitalizations due to COPD, the number of emergency room visits and hospitalizations combined due to COPD, the number of unscheduled outpatient visits due to COPD and the number of all unscheduled healthcare encounters due to COPD experienced by a subject during the 56-week double-blind treatment period will be used as response variables in four different statistical models with the logarithm of the subject's corresponding follow-up time used as an offset in the analysis to adjust for subjects having different exposure times similar to COPD exacerbations as described in section 8.4.1.5. If multiple healthcare encounters are associated with one COPD exacerbation all the encounters will be counted for this endpoint.

8.4.2   Calculation or derivation of safety variable(s)

8.4.2.1   Safety variables

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

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

8.4.2.2   Other significant adverse events

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

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

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

8.4.3   Calculation or derivation of patient reported outcome variables

SGRQ

Potential health status treatment benefits of benralizumab will be evaluated by comparing the change from baseline at Week 56 in SGRQ Total scores. For the responder analysis of SGRQ

a responder will be defined as an individual with a ≥4-point decrease (improvement) in SGRQ total score at Week 56.

E-RS

Respiratory symptoms will be evaluated using the E-RS. Individual daily E-RS total and subscale scores will be calculated and summarized as a biweekly (14 day) mean. Data collected in the two-week period prior to randomisation will be used to calculate the individual E-RS total and subscale baseline means.

EXACT-PRO

The number, average duration, and severity of EXACT-PRO defined events will be evaluated. EXACT-PRO daily total scores as well as domain scores will be calculated according to the developer approved scoring algorithm. The total score will be used to identify event onset and recovery as well as the magnitude (severity) of the event. The baseline total score will be the mean within subject score over the 7 days prior to randomisation. A minimum of 4 days of data is required for calculating the baseline total score. To allow for improvement or deterioration in disease state over the course of the trial, the baseline total score should be reset every 4 weeks in the absence of an EXACT-PRO defined event. Event frequency is calculated by comparing the baseline with daily total scores. Calculating event duration requires identification of the following five parameters: 1) onset; 2) three-day rolling average; 3) maximum observed value; 4) threshold for improvement; and 5) recovery. The severity of an event is indicated by the worst (highest) EXACT-PRO total score during an event. Complete details concerning variable calculation are provided in the scoring manual and will be provided in the study Statistical analysis plan (SAP).

BDI/TDI

The instrument consists of three components: functional impairment, magnitude of task, and magnitude of effort. For the BDI, each of these three components are rated in five grades from 0 (severe) to 4 (unimpaired), and are summed to form a baseline total score from 0 to 12. The BDI will be captured at baseline only. For the TDI, changes in dyspnea are rated for each component by seven grades from -3 (major deterioration) to +3 (major improvement), and are added to form a total TDI score from -9 to +9.

8.4.4 Calculation or derivation of pharmacokinetic variables

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

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

8.4.5 Calculation or derivation of immunogenicity variables

ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer). The presence of anti-benralizumab antibodies is determined relative to a cutoff value that is calculated for each plate as the mean response of the negative control wells multiplied by a cut point factor. The cut point factor was statistically determined during assay validation. Samples that measure at or above the cut point value are considered as potential positives for ADA and are retested in a confirmatory (specificity) assay, both in the absence and presence of excess benralizumab. Samples are confirmed to be positive for ADA if the percent inhibition of response in the presence of benralizumab is greater than or equal to the confirmatory cut point established during assay validation. Confirmed positive samples are then measured in a titer assay. Titers are performed by serially diluting samples with negative control serum and are reported as the reciprocal of the highest dilution (over the 1:50 minimum required sample dilution) that measure positive in the assay, before returning a negative response.

Neutralizing antibody (nAb) evaluations will be conducted on those serum samples that test positive for ADA at end of treatment and also during the study follow up period. ADA-positive samples will retested in a competitive ligand-binding assay to determine if the ADA present is capable of inhibiting (neutralizing) the binding of benralizumab to soluble recombinant human interleukin 5 receptor (IL-5R). The test sample is deemed positive or negative for the presence of neutralizing antibodies (nAb) to benralizumab relative to a pre-determined (in assay validation), statistically derived cut point. Samples positive for nAb to benralizumab are then titered to determine relative amounts of nAb present in each test sample.

8.5 Methods for statistical analyses

The primary analysis of the primary and key secondary endpoints will include all data captured during the 56-week treatment period, regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence.

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.

Testing strategy to account for multiplicity considerations

To account for multiplicity to test the primary (exacerbation) and two key secondary endpoints (FEV$_1$ and SGRQ) for each of the 30mg and 100mg dose groups (for subjects with baseline blood eosinophils $\geq$220/μL) a testing strategy will be followed to control the overall type I error rate at level 0.05. The testing strategy will be according to the following gate keeping procedure:

Step 1: Perform the two tests of annual COPD exacerbation rate (one test for each dose vs. placebo) at the family wise error rate (FWER) of 0.04 using a Hochberg Procedure (Hochberg

1988). If both p-values are less than 0.04, then proceed to Step 2; else if the smaller p-value is less than 0.02 then proceed to Step 2a; otherwise no null hypothesis is rejected

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

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

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The gatekeeping procedure is also shown in the diagram below:

Figure 4   Gatekeeping Procedure
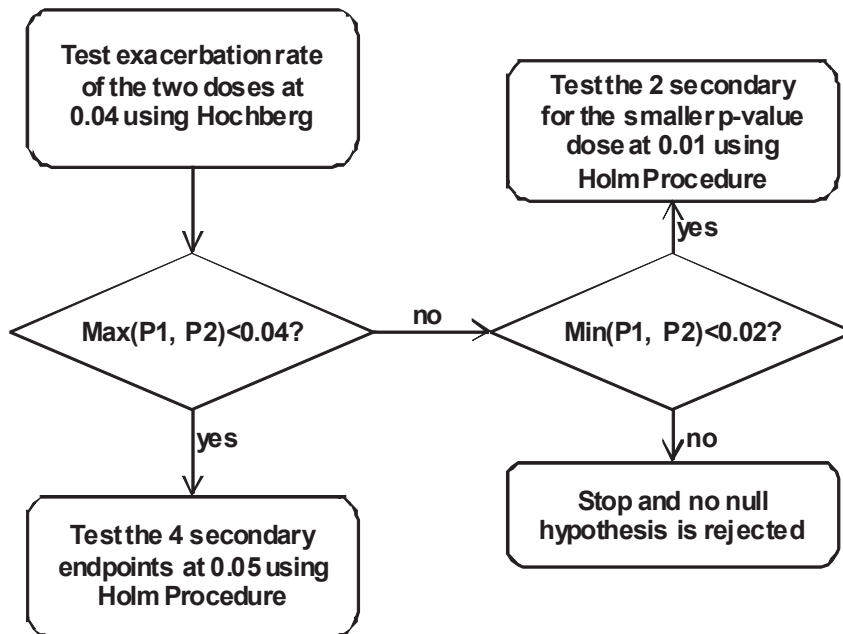
Since the correlation of the two test statistics for COPD exacerbation rate in the Step 1 is positive, the FWER of the Hochberg Procedure is strongly controlled at 0.04. The overall FWER of the gatekeeping procedure is strongly controlled at 0.05.

For the comparison of the 10mg dose group and placebo in subjects with baseline blood eosinophils ≥300/μL, multiplicity will be adjusted for the testing of the primary and two key secondary endpoints using a serial gatekeeping procedure (Dmitrienko and Tamhane 2007). In the procedure the primary endpoint will be tested at 0.05 level for the comparison of the 10mg dose group and placebo. The two secondary endpoints will be tested using a Holm procedure at the 0.05 level for the comparison of the 10mg dose group and placebo only if the test for the primary endpoint is significant at 0.05 level.

In summary the FWER will be strongly controlled for the comparison of 30mg and 100mg vs. placebo at 0.05 on testing of the primary endpoint and two key secondary endpoints. The FWER will also be strongly controlled for the comparison of 10mg vs. placebo at 0.05 on

testing of the primary endpoint and two key secondary endpoints. The FWER will not be strongly controlled at 0.05 for the testing of the primary endpoint and two key secondary endpoints across all three doses.

8.5.1 Primary analysis method(s)

The primary efficacy variable is the annual COPD exacerbation rate and the primary analysis is to compare the annual COPD exacerbation rate of each benralizumab dose group with placebo in subjects with baseline blood eosinophil counts ≥220/µL.

For each of the three benralizumab dose groups, 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, i.e.:

H0: Rate ratio (benralizumab vs. Placebo) = 1

Ha: Rate ratio (benralizumab vs. Placebo) ≠ 1

Exacerbation rate in each of the three benralizumab dose groups will be compared to exacerbation rate in the placebo group using a negative binomial model. The response variable in the model will be the number of COPD exacerbations over the 56-week treatment period. The model will include covariates of treatment group, eosinophil cohort (220-299/µL or ≥300/µL), country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and the number of exacerbations in the year before the study. 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 subjects with baseline blood eosinophil counts <220/µL, <150/µL, 150-219/µL, 220-299/µL, 300-449/µL, and ≥450/µL separately for descriptive purpose only.

8.5.2 Secondary analysis methods

8.5.2.1 Analysis methods for secondary efficacy variables

Key secondary efficacy endpoints in this study are:

- Change from baseline in pre-dose/pre-bronchodilator FEV_1 at Week 56

- Change from baseline in SGRQ total score at Week 56

Other secondary efficacy endpoints include

- Proportion of subjects with ≥1 COPD exacerbation

– Time to the first COPD exacerbation

– Proportion of subjects with ≥4-point decrease (improvement) in SGRQ total score at Week 56

– Annual rate of COPD exacerbations that are associated with an emergency room visit or a hospitalization

– Annual rate of hospitalizations, annual rate of hospitalizations and emergency room visits combined, annual rate of unscheduled outpatient visits including unscheduled visits to study centres and all unscheduled healthcare encounters due to COPD

– Rescue medication use (average puffs/day)

– Number of nights with awakening due to COPD and requiring rescue medication

– Change from baseline in E-RS total score and domain scores at Week 56

– Area under the curve (AUC) of E-RS total score

– BDI/TDI

– CAT

– EXACT-PRO

All the secondary efficacy endpoints will be analyzed in subjects with baseline blood eosinophil counts ≥220/µL. In addition, the two key secondary endpoints will also be summarized in subjects with baseline blood eosinophil counts <220/µL, <150/µL, 150-219/µL, 220-299/µL, 300-449/µL, and ≥450/µL separately for descriptive purpose only.

Change from baseline in pre-dose/pre-bronchodilator FEV_1 at Week 56 will be compared between each of the three benralizumab dose groups and placebo using a repeated measures analysis on subjects with a baseline pre-dose/pre-bronchodilator FEV_1 and at least one post-randomisation pre-dose/pre-bronchodilator FEV_1 in the full analysis set. The dependent variable will be the change from baseline in pre-bronchodilator FEV_1 at post-baseline protocol-specified visits (up to the EOT visit). Treatment group will be fitted as the explanatory variable, and eosinophil cohort (220-299/µL or ≥300/µL), country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), visit, the interaction between visit and treatment and baseline pre-bronchodilator FEV_1 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+ eosinophil cohort (220-299/µL or ≥300/µL) + baseline FEV_1+ country + background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA) + visit + treatment*visit

Change from baseline in SGRQ total score and three domain scores (symptoms, activity, and impacts) at Week 56 will be analyzed separately using a similar model as the above model for change from baseline in pre-dose/pre-bronchodilator FEV_1.

Proportion of subjects with ≥4-point decrease (improvement) in SGRQ total score at Week 56 in each of the three benralizumab dose groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for eosinophil cohort (220-299/µL or ≥300/µL), country, and background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA). Cumulative distribution function of absolute changes in SGRQ total score at week 56 will be plotted in a figure.

The proportion of subjects with ≥1 COPD exacerbation during the 56 weeks of treatment will be addressed as a supportive variable to the primary objective. The proportion in each of the three benralizumab dose groups will be compared with the proportion in the placebo group using a logistic regression model with eosinophil cohort (220-299/µL or ≥300/µL), country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and number of exacerbations in the year before the study as covariates.

Time to first COPD exacerbation will be analyzed as another supportive efficacy variable to the primary objective to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment, eosinophil cohort (220-299/µL or ≥300/µL), country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and number of exacerbations in the year before the study.

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

Annual rates of hospitalizations, hospitalizations and emergency room visits combined, unscheduled outpatient visits including unscheduled visits to study centres as well as all unscheduled healthcare encounters due to COPD (hospitalizations, emergency room visits, and unscheduled outpatient visits including unscheduled visits to study centres) will be analyzed using Negative Binomial Models as outlined for the primary efficacy variable in section 8.5.1.

The number of nights with awakening due to COPD and requiring rescue medication will be analyzed as the response variable by fitting a repeated measures model to data. Treatment group will be fitted as the explanatory variable, and eosinophil cohort (220-299/µL or ≥300/µL), country, baseline value and background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA) will be fitted as covariates. Rescue medication use (average puffs/day) will be analyzed using a similar model.

Change from baseline in E-RS total score and domain scores at Week 56 will be analyzed separately using a similar model as the model for change from baseline in pre-dose/pre-bronchodilator FEV_1. AUC of E-RS total score will be analyzed by fitting an ANCOVA model with treatment, eosinophil cohort (220-299/μL or $\geq$300/μL), country, baseline value, and background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA) as covariates.

The BDI/TDI, EXACT-PRO, and CAT will be summarized by treatment and visit.

8.5.2.2 Analysis methods for safety variables

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

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

8.5.2.3 Analysis Methods for PK Variables

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

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

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

8.5.2.4 Analysis Method for Immunogenicity Variables

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

will be generated. The impact of ADA on PK and eosinophil level will be assessed. The potential association of ADA with safety and efficacy will be evaluated. The association of the nAb titer with the ADA titer, benralizumab concentration, blood eosinophil levels, and asthma exacerbation rate will be evaluated for ADA positive subjects only.

8.5.3   Exploratory analysis

An exploratory objective of this study is to understand the dose-response relationship. This will be explored through modelling the dose response for the primary and key secondary endpoints across all 3 benralizumab dose levels (10mg, 30mg, and 100mg).

Analysis for the other exploratory objectives will be specified in the SAP.

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 the SAP and documented prior to database lock of the studies.

8.5.5   Subgroup analysis

Details of all subgroup analyses and statistical modeling including possible testing of interaction between treatment group and covariates will be described in the SAP.

8.5.6   Interim Analysis

The futility analysis will be based on the pooled data of study D3251C00003 and study D3251C00004 when approximately 15% patients with baseline blood eosinophil counts ≥220/μL have completed the studies. The percentage of patients is based on the total number of patients with eosinophil counts ≥220/μL expected to be recruited in the studies. In the futility analysis, decision will be based on the comparison of the futility boundary and the estimated exacerbation rate reductions of benralizumab doses vs. placebo in patients with eosinophil counts ≥220/μL from the negative binomial model as documented for the final analysis in section 8.5.1. Futility will be declared if the higher exacerbation rate reduction of benralizumab 30mg vs. placebo and benralizumab 100mg vs. placebo is less than 8%. A futility boundary of 8% was chosen based on the operating characteristics of ~55% chance of stopping the study for futility under the null hypothesis of equal exacerbation rates across all treatments and ~2% chance of stopping the study for futility assuming an exacerbation rate reduction of 30% for both benralizumab doses vs. placebo. Full details about the futility analysis decision rules and procedures will be specified in an IDMC charter and the charter will also specify the roles and responsibilities of the IDMC members. A firewall will be established to ensure the maintenance of the study blind for the sponsor, the investigational site staff and patients. Further the IDMC charter will specify the timing of analysis and the expected extent of data available at the time of interim analysis. Conducting a futility analysis

results in power loss. The sample size calculation in section 8.2 has accounted for this loss and the study has 90% of power under the powering assumptions and the futility boundary of 8%.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study centre personnel

Before the first subject 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 the WBDC and ePROs system(s) 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 eCRFs, 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 eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

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

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Recording of data

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

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

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

9.2.3 Study agreements

The Principal Investigator at each/the 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 subjects and in all other respects, not relating to study conduct or treatment of subjects, 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 subjects are enrolled.

9.2.4 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study is expected to start in Q2 2014 and to end by Q4 2017.

The study may be terminated at individual 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.

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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.

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

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 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 study Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process

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.

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 laboratories 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 Subject data protection

The Informed Consent 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 subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

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

10.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. 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 subject into the study.

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

AstraZeneca should approve any modifications to the Informed Consent 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 subject into the study, the final study protocol, including the final version of the Informed Consent 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, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

For the US and Canada, may also be applicable to other countries, Each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4   Informed consent

The Principal Investigator(s) or designee at each centre will:

–   Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study

–   Ensure each subject is notified that they are free to discontinue from the study at any time

–   Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided

–   Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study

–   Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File

–   Ensure a copy of the signed Informed Consent Form is given to the subject

Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

10.5   Changes to the protocol and informed consent form

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

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

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

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

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the 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 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 about an inspection at the centre.

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Clinical Study Protocol Amendment

Amendment Number   3

Drug Substance   Benralizumab (MEDI-563)

Study Code   D3251C00004

Date   03 July 2015

Protocol Dated   11 February 2015

A Randomised, Double-blind, Double Dummy, Chronic Dosing (56 week) Placebo-controlled, Parallel Group, Multicentre, Phase III Study to Evaluate the Efficacy and Safety of 3 Doses of Benralizumab (MEDI-563) in Patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) with a History of COPD Exacerbations (TERRANOVA)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

This protocol amendment affects all the centers participating in this study.

The protocol for the study is to be amended as follows:

Section of protocol affected:

Protocol synopsis, Study centre(s) and number of subjects planned

Previous text:

Approximately 300 study centres worldwide in 21 countries will randomise a total of 2088 subjects.

Revised text:

Approximately **380** study centres worldwide in **24** countries will randomise a total of **2168** subjects.

Reason for Amendment:

This change reflects updated sample size estimate, change in approximate number of participating centres and countries.

Persons who initiated the Amendment:

Redacted , Global Product Statistician Delegate

Redacted , Clinical Development Manager

Section of protocol affected:

Protocol synopsis, Study Design

1.4   Overall Study Design

3.3   Subject Enrolment and Randomisation

Previous text:

The study will recruit approximately 2088 subjects randomised 1:1:1:1 to the treatment arms, stratified by country and blood eosinophil count and randomised in a 2:1 ratio to the $\geq 300/\mu L$ and $<300/\mu L$ eosinophil strata. The subject recruitment will be capped at a country and/or site level according to eosinophil count ($\geq 300/\mu L$ and $<300/\mu L$) via the interactive web/voice response system (IWRS/IVRS). Once a stratum is filled, subjects will no longer be randomised to that stratum.

Revised text:

The study will recruit approximately **2168** subjects randomised 1:1:1:1 to the treatment arms, stratified by country and blood eosinophil count **($\geq 300/\mu L$ and $<300/\mu L$ strata)**. The subject recruitment will be capped **at the study level for the cohorts with baseline eosinophil counts $<220/\mu L$, 220-299/μL, and $\geq 300/\mu L$ in order to keep predefined cohort sample size and approximately 2:1 ratio of subjects above and below the boundary of 220/μL. Details**

2(22)

of the estimated numbers of recruited subjects/arm in each cohort (<220/µL, 220-299/µL, ≥300/µL) are described in the SAP.

Reason for Amendment:

This change reflects the new eosinophil boundary of ≥220/µL, the details of the new eosinophil cohorts, and the updated sample size estimate.

Persons who initiated the Amendment:

Redacted , Global Product Statistician Delegate

Section of protocol affected:

Protocol synopsis, Statistical Methods

Previous text:

The primary efficacy variable is the annual COPD exacerbation rate and the two key secondary endpoints are change from baseline in pre-dose/pre-bronchodilator FEV1 at Week 56 and also change from baseline in St. George's Respiratory Questionnaire (SGRQ) at Week 56. The exacerbation rate in each of the three benralizumab dose groups will be compared to the exacerbation rate in the placebo group using a negative binomial model including covariates of treatment group, country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and the number of exacerbations in the year before the study. The logarithm of the follow-up time will be used as an offset variable in the model. Change from baseline in pre-dose/pre-bronchodilator FEV1 at Week 56 will be compared between each of the three benralizumab dose groups and placebo using a repeated measures analysis. Treatment group will be fitted as the explanatory variable. Country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and baseline pre-bronchodilator FEV1 will be fitted as covariates. Visit will be fitted as a categorical variable.

…

The primary endpoint and the two key secondary endpoints will be analyzed primarily using the subjects with baseline blood eosinophil counts ≥300/µL in the full analysis set. The full analysis set includes all randomised subjects who received any dose of investigational product. In addition, the exacerbation rate and the two key secondary endpoints will also be summarized in subjects with baseline blood eosinophil counts <300/µL, <150/µL, 150-299/µL, 300-449/µL, and ≥450/µL separately for descriptive purpose only.

Multiplicity will be adjusted for the primary endpoint and the two key secondary endpoints on the analysis of subjects with baseline blood eosinophils ≥300/µL for the comparisons of 30mg vs. placebo and 100mg vs. placebo according to a gatekeeping procedure (see section 8.5). Multiplicity will also be adjusted for the primary endpoint and the two key secondary endpoints on the analysis of subjects with baseline blood eosinophils ≥300/µL for the

comparisons of 10mg vs. placebo according to a serial gatekeeping procedure (see section 8.5).

The study will recruit subjects with blood eosinophil counts ≥300/µL and <300/µL at a ratio of 2:1 and the study is powered for the primary efficacy analysis of the subjects with blood eosinophils ≥300/µL. For the primary endpoint annual COPD exacerbation rate, 348 subjects with baseline blood eosinophil counts ≥300/µL per treatment arm (1392 total) will need to be randomised to achieve 90% power of detecting a 30% reduction in both the 30mg and 100mg benralizumab dose groups versus placebo after multiplicity adjustment. This calculation has assumed two-sided 4% alpha level test, an annual placebo rate of 0.93 events/subject (1.0 events/subject/56 weeks), a negative binomial shape parameter of 0.4, and a dropout rate of 10%. The sample size calculation is based on simulations and has accounted for the power loss from a proposed futility analysis. According to the 2:1 ratio, the study will also enrol 174 subjects/arm (696 total) with baseline blood eosinophil counts <300/µL. So a total of 2088 subjects are expected to be randomised in the study.

An unblinded futility analysis based on the primary endpoint will be conducted in this study. The futility analysis will be carried out using pre-defined rules by an external Independent Data Monitoring Committee in order to ensure the integrity of the blinded nature of the study. Furthermore, an internal blinded estimate of the overall exacerbation rate and shape parameter will be conducted before the last subject with eosinophil counts ≥300/µL is randomised. The review may result in an adjustment to the sample size.

Revised text:

The primary efficacy variable is the annual COPD exacerbation rate and the two key secondary endpoints are change from baseline in pre-dose/pre-bronchodilator FEV1 at Week 56 and also change from baseline in St. George's Respiratory Questionnaire (SGRQ) at Week 56. The exacerbation rate in each of the two benralizumab dose groups will be compared to the exacerbation rate in the placebo group using a negative binomial model including covariates of treatment group, **eosinophil cohort (220-299/µL or ≥300/µL)**, country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and the number of exacerbations in the year before the study. The logarithm of the follow up time will be used as an offset variable in the model. Change from baseline in pre-dose/pre-bronchodilator FEV1 at Week 56 will be compared between each of the three benralizumab dose groups and placebo using a repeated measures analysis. Treatment group will be fitted as the explanatory variable. **Eosinophil cohort (220-299/µL or ≥300/µL)**, country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and baseline pre-bronchodilator FEV1 will be fitted as covariates. Visit will be fitted as a categorical variable.

…

The primary endpoint and the two key secondary endpoints will be analyzed primarily using the subjects with baseline blood eosinophil counts **≥220/µL** in the full analysis set. The full analysis set includes all randomised subjects who received any dose of investigational product. In addition, the exacerbation rate and the two key secondary endpoints will also be

summarized in subjects with baseline blood eosinophil counts **<220/µL,** <150/µL, **150-219/µL, 220-299/µL,** 300-449/µL, and ≥450/µL separately for descriptive purpose only.

Multiplicity will be adjusted for the primary endpoint and the two key secondary endpoints on the analysis of subjects with baseline blood eosinophils **≥220/µL** for the comparisons of 30mg vs. placebo and 100mg vs. placebo according to a gatekeeping procedure (see section 8.5). Multiplicity will also be adjusted for the primary endpoint and the two key secondary endpoints on the analysis of subjects with baseline blood eosinophils **≥220/µL** for the comparisons of 10mg vs. placebo according to a serial gatekeeping procedure (see section 8.5).

The study will recruit subjects with blood eosinophil counts **≥220/µL and <220/µL** at a ratio of **approximately** 2:1 and the study is powered for the primary efficacy analysis of the subjects with blood eosinophils **≥220/µL**. For the primary endpoint annual COPD exacerbation rate, 348 subjects with baseline blood eosinophil counts **≥220/µL** per treatment arm (1392 total) will need to be randomised to achieve 90% power of detecting a 30% reduction in both benralizumab dose groups versus placebo after multiplicity adjustment. This calculation has assumed two-sided 4% alpha level test, an annual placebo rate of 0.93 events/subject (1.0 events/subject/56 weeks), a negative binomial shape parameter of 0.4, and a dropout rate of 10%. The sample size calculation is based on simulations and has accounted for the power loss from a proposed futility analysis. According to the **approximately** 2:1 ratio, the study will also enrol 174 subjects/arm (696 total) with baseline blood eosinophil counts **<220/µL. An additional 20 subjects/arm will also be recruited to the 220-299/µL cohort to better characterize patients within this cohort. This addition results in 368 subjects/arm in the ≥220/µL cohort (1472 total). A total of 2168 subjects are expected to be randomised in the study. Details of the estimated numbers of recruited subjects/arm in each cohort (<220/µL, 220-299/µL, ≥300/µL) are described in the SAP.**

An unblinded futility analysis based on the primary endpoint will be conducted in this study. The futility analysis will be carried out using pre-defined rules by an external Independent Data Monitoring Committee in order to ensure the integrity of the blinded nature of the study. Furthermore, an internal blinded estimate of the overall exacerbation rate and shape parameter will be conducted before the last subject with eosinophil counts **≥220/µL** is randomised. The review may result in an adjustment to the sample size.

Reason for Amendment:

This change reflects 1) the new eosinophil boundary of ≥220/µL for the primary and key secondary efficacy endpoints, 2) the inclusion of an additional covariate – eosinophil cohort (220-299/µL or ≥300/µL) – in the statistical analysis models, and 3) the updated sample size estimates.

Persons who initiated the Amendment:

Redacted , Global Product Statistician Delegate

Section of protocol affected:

1.2   Rationale for study design, doses and control groups

Previous text:

The final results of study MI-CP196 support conducting this Phase 3 study in patients with COPD with severe and very severe disease, treated with double (ICS/LABA, LABA/LAMA) and triple therapy (ICS/LABA/LAMA), who have elevated peripheral eosinophils. The greatest improvements in the annual exacerbation rate were observed in patients with blood eosinophils ≥300/µL based on a pre-specified subgroup analysis (predose FEV1 and health-related quality of life as measured by SGRQ-C). In patients with low eosinophil counts (<300/µL), the exacerbation signal was not commensurate with what was observed in the high eosinophil group, and the exacerbation rate was not favourable for benralizumab, although the changes in FEV1 and SGRQ-C were directionally similar to the high eosinophil group.

…

Subjects with high (≥300/µL) and low (<300/µL) blood eosinophils will be enrolled and stratified in this Phase 3 study in a 2:1 ratio. Based on the efficacy observed in CP196, the primary endpoint will be powered and conducted in the high (≥300/µL) blood eosinophil group. Subjects with low (<300/µL) blood eosinophils will be included to assess the benefit:risk relationship of benralizumab in COPD based on blood eosinophil levels. Descriptive statistics will be used to assess efficacy in COPD subjects with low (<300/µL) blood eosinophils.

Revised text:

The final results of study MI-CP196 support conducting this Phase 3 study in patients with COPD with severe and very severe disease, treated with double (ICS/LABA, LABA/LAMA) and triple therapy (ICS/LABA/LAMA), who have elevated peripheral eosinophils. The greatest improvements in the annual exacerbation rate were observed in patients with **increasing** blood eosinophils (**specifically ≥200 and ≥300/µL**) based on a pre-specified subgroup analysis (predose FEV1 and health-related quality of life as measured by SGRQ-C). In patients with low eosinophil counts (<300/µL), the exacerbation signal was not commensurate with what was observed in the high eosinophil group, and the exacerbation rate was not favourable for benralizumab, although the changes in FEV1 and SGRQ-C were directionally similar to the high eosinophil group.

…

Subjects in this Phase 3 study will be stratified by country and blood eosinophil levels (≥300/µL or <300/µL) with a blood eosinophils boundary of ≥220/µL used for the primary and secondary efficacy analyses. Randomization will be capped at the study level for the baseline eosinophil cohorts (<220/µL, 220-299/µL, ≥300/µL) in order to keep predefined cohort sample size and approximately 2:1 ratio of subjects above and below the boundary of 220/µL.

Based on the efficacy observed in CP196 and recent data in the literature (Pascoe S et al 2015), the primary endpoint will be powered and conducted in subjects with blood eosinophil count ≥220/µL. Subjects with lower blood eosinophils levels (<220/µL) will be included to assess the benefit: risk relationship of benralizumab in COPD patients with a broad range of blood eosinophil levels. Descriptive statistics will be used to assess efficacy in COPD subjects across a broad spectrum of eosinophil levels as detailed in the SAP in order to better identify patients who are likely to benefit from benralizumab and also to evaluate inflection points for efficacy and safety to better define which patients need to be treated with this compound.

Reason for Amendment:

The change reflects ongoing literature which suggests an eosinophil driven phenotype is likely present in patients who have >150/µL, and to establish the need to recruit a cohort with blood eosinophils ≥220/µL, which will now will be considered the boundary of the primary analysis.

Persons who initiated the Amendment:

Redacted , Senior Director Inflammation Neuroscience and Respiratory

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Section of protocol affected:

1.3   Benefit/risk and ethical assessment

Previous text:

In a previous study patients who had an eosinophil count ≥300 appeared to have the greatest benefit from the drug and remained the main target of the study. The exacerbation rate reduction was not evident in the <300 eosinophil group, therefore the study will include patients above and below the 300 eosinophil cut off in a 2:1 ratio. This will allow exploring the benefit risk profile in the broader population.

Revised text:

In a previous study patients who had an eosinophil count ≥300 appeared to have the greatest benefit from the drug and remained the main target of the study. The exacerbation rate reduction was not evident in the <300 eosinophil group **although the sample size was small. In order to better identify the eosinophil threshold for predicted response to Benralizumab, and based on recent data in the literature (Pascoe S et al 2015) to support a boundary of 220/µL for the primary analysis, additional patients will be recruited to a ≥220/µL in addition to the ≥300/µL blood eosinophil cohort in this study. This will result in including patients above and below the 220 eosinophil cut-off in an approximately 2:1 ratio, allowing for exploration of the benefit risk profile in the broader population.**

Reason for Amendment:

The change reflects ongoing literature which suggests an eosinophil driven phenotype is likely present in patients who have >150/μL, and to establish the need to recruit a cohort with blood eosinophils >220/μL, which will now will be considered the boundary of the primary analysis.

Persons who initiated the Amendment:

Redacted , Senior Director Inflammation Neuroscience and Respiratory

Section of protocol affected:

3.1   Additional criteria to be checked prior to randomisation:
        Inclusion criteria #11

Previous text:

Blood eosinophils due to subject's stratification for blood eosinophil levels. When either eosinophil stratum (≥300μL or <300μL) is full, subjects in the completed stratum will not be randomised and will be withdrawn from the study (see section 3.7.2).

Revised text:

Blood eosinophils due to subject's stratification **and cap** for blood eosinophil levels. When **any eosinophil cohort (<220/μL, 220-299/μL, or ≥300/μL)** is full, subjects in the completed **cohort** will not be randomised and will be withdrawn from the study (see section 3.7.2).

Reason for Amendment:

The change reflects accommodation of the 220-299 cohort and the resulting change in the cohort closure strategy.

Persons who initiated the Amendment:

Redacted , Senior Director Inflammation Neuroscience and Respiratory

Section of protocol affected:

3.2   Exclusion criteria #26

Previous text:

Subjects who in the opinion of the investigator or qualified designee have evidence of active tuberculosis (TB), either treated or untreated, or latent TB without completion of an appropriate course of treatment or appropriate ongoing treatment. Evaluation will be according to the local standard of care and may consist of history and physical examinations,

chest x-ray, and/or TB test (eg purified protein derivative testing etc with the standard of care as determined by local guidelines).

Revised text:

Subjects who in the opinion of the investigator or qualified designee have evidence of active tuberculosis (TB). **Subjects with a recent (within 2 years) first-time or newly positive purified protein derivative (PPD) test or Quantiferon test need to complete an appropriate course of treatment before being considered for enrolment. Evaluation will be according to the local standard of care and may consist of history and physical examinations, chest x-ray, and/or TB test as determined by local guidelines.**

Reason for Amendment:

To specifically clarify that patients with newly or first time positive test need to be treated according to guidelines in order to be considered for enrolment. The amendment was also put in place to remove unclear language in regards to latent tuberculosis.

Persons who initiated the Amendment:

Redacted   Senior Director Inflammation Neuroscience and Respiratory

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Section of protocol affected:

3.3   Subject Enrolment and Randomisation

Previous text:

It is expected that the <300/μL stratum will fill first based on prevalence.

Revised text:

It is expected that the **<220/μL cohort** will fill first based on prevalence.

Reason for Amendment:

This change reflects the new eosinophil boundary of ≥220/μL.

Persons who initiated the Amendment:

Redacted   , Global Product Statistician Delegate

Section of protocol affected:

3.7.2   Withdrawal due to recruitment completion in a randomisation stratum

Previous text:

3.7.2   Withdrawal due to recruitment completion in a randomisation stratum

When either eosinophil stratum ≥300/μL or <300/μL is full, subjects in the completed stratum will not be randomised and will be withdrawn from the study.

Revised text:

3.7.2   Withdrawal due to recruitment completion in an **eosinophil cohort**

When **any** eosinophil **cohort (<220/μL, 220-299/μL, or ≥300/μL)** is full, subjects in the completed **cohort** will not be randomised and will be withdrawn from the study.

Reason for Amendment:

The change reflects accommodation of the 220-299 cohort and the resulting change in the cohort closure strategy.

Persons who initiated the Amendment:

Redacted   , Senior Director Inflammation Neuroscience and Respiratory

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Section of protocol affected:

4.   STUDY PLAN AND PROCEDURES

Table 3   Study Plan – Randomisation, treatment period and follow-up

Previous text:

f   nAb will be assessed at week 56 (primary end point) and week 60 or at the discontinuation EOT visit

Revised text:

f   nAb will be assessed **on all ADA positive samples. Samples that are ADA negative will not be tested for nAb.**

Reason for Amendment:

nAB titer removed as not being run and replaced by nAb phenotype (positive/negative).

Persons who initiated the Amendment:

Redacted   , Fellow/Scientific Director Translational Sciences Clinical Pharmacology and DMPK

Section of protocol affected:

4.1.1   Enrolment (from Visit 1 to Visit 2)

Previous text:

Enrolment procedures when low (<300/μL) eosinophil stratum is closed

As soon as the low (<300/uL) eosinophil stratum is closed at a site or country level, it is recommended to split enrolment procedures between Visit1 and Visit 2 (as described in Table 2) and to allow sufficient time between Visit 1 and Visit 2 (up to 7 days) to obtain central eosinophil blood count results. The subjects with blood eosinophil count <300/μL will be withdrawn from the study (screen failure), no further study related procedures are required for those subjects (see section 3.7.2).

Revised text:

Enrolment procedures when **any** of the eosinophil **cohorts** is closed

As soon as **any of the eosinophil cohorts is closed**, it is recommended to split enrolment procedures between Visit1 and Visit 2 (as described in Table 2) and to allow sufficient time between Visit 1 and Visit 2 (up to 7 days) to obtain central eosinophil blood count results. The subjects **in the completed cohort** will be withdrawn from the study (screen failure), no further study related procedures are required for those subjects (see section 3.7.2).

Reason for Amendment:

Amended to specify a sequence of enrolment procedures when any eosinophil cohort is closed.

Persons who initiated the Amendment:

Redacted , Clinical Research Physician

Section of protocol affected:

4.1.3   Rescreening

Additional text:

One additional re-screening may be allowed for patients who have been screen failed due to eosinophil stratum/ cohort closure; those instances need to be discussed with the AZ Study Physician.

Reason for Amendment:

The change introduces an additional re-screening option for patients with borderline blood eosinophil levels and takes into account changes to eosinophil cohort boundaries.

Persons who initiated the Amendment:

Redacted , Senior Director Inflammation Neuroscience and Respiratory

Section of protocol affected:

5.3.1   Central Laboratory Eosinophil Testing

Previous text:

Subjects will be stratified by the absolute blood eosinophil count as assessed by a central laboratory (haematology sample taken at Visit 1, see section 5.2.6), with the aim of randomising subjects with ≥300/µL versus those with <300/µL in a ratio of 2:1. Once a stratum is filled, subjects allocated to that particular stratum based on the Visit 1 eosinophil count, will be screen failed (see section 3.7.2).

Revised text:

Subjects will be stratified by the absolute blood eosinophil count as assessed by a central laboratory (haematology sample taken at Visit 1, see section 5.2.6), **and randomization will be capped at the study level for the baseline eosinophil cohorts (<220/µL, 220-299/µL, ≥300/µL) in order to keep predefined cohort sample size and approximately 2:1 ratio of subjects above and below the boundary of 220/µL**. **Once any of the eosinophil cohorts** is filled, subjects allocated to that particular **cohort** based on the Visit 1 eosinophil count, will be screen failed (see section 3.7.2).

Reason for Amendment:

The change reflects accommodation of the new blood eosinophil boundary of 220/µL for the primary analysis and the new 220-299/µL cohort.

Persons who initiated the Amendment:

Redacted   Senior Director Inflammation Neuroscience and Respiratory

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Section of protocol affected:

5.3.5.2 Immunogenicity

Previous text:

Neutralizing antibodies (nAb)

Neutralizing antibodies (nAb) will be assessed at week 56 (end of treatment) and on week 60 (final follow-up) as well as at any discontinuation EOT visit.

Revised text:

Neutralizing antibodies (nAb)

Neutralizing antibodies (nAb) will be assessed **on all ADA positive samples. ADA negative samples will not be tested for nAb**.

Reason for Amendment:

nAB titer removed as not being run and replaced by nAb phenotype (positive/negative).

Persons who initiated the Amendment:

Redacted , Fellow/Scientific Director Translational Sciences Clinical Pharmacology and DMPK

Section of protocol affected:

8.2   Sample size estimate

Previous text:

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

For the primary endpoint annual COPD exacerbation rate, 348 subjects with baseline blood eosinophil counts ≥300/µL per treatment arm (1392 total) will need to be randomised to achieve 90% power of detecting a 30% reduction in both the 30mg and 100mg benralizumab dose groups versus placebo based on a Hochberg Procedure (Hochberg 1988). This calculation has assumed two-sided 4% alpha level tests, an annual placebo rate of 0.93 events/subject (1.0 events/subject/56 weeks), a negative binomial shape parameter of 0.4, and a dropout rate of 10%. The sample size calculation is based on simulations and has accounted for the power loss from a proposed futility analysis (Section 8.5.6).

As stated previously a 2:1 ratio will be used for subjects with blood eosinophil counts ≥300/µL and <300/µL. Therefore this study will randomise 174 subjects/arm (696 total) with baseline blood eosinophil counts <300/µL. A total of 2088 subjects are expected to be randomised in this study.

The sample size necessary to achieve a stated power (90% in our case) in this study is calculated based on the estimate of overall exacerbation rate and shape parameter from the negative binomial model (Section 8.5.1). In order to better estimate the overall exacerbation rate and shape parameter, we plan to conduct a single blinded sample size re-estimation in both studies D3251C0003 and D3251C0004. Blinded estimates of the overall exacerbation rate as well as the shape parameter from data pooled across placebo and all benralizumab doses (for patients with eosinophil counts ≥300/µL) will be used in the sample size re-estimation and strictly no treatment information will be used in the review. The pooled study summaries will not contain any information that would potentially reveal the treatment assignments (e.g., post-randomization eosinophil levels). The review will be conducted before the last patient with eosinophil counts ≥300/µL is randomized and after the futility analysis

(Section 8.5.6). The exacerbation rate and shape parameter will be estimated using the maximum likelihood approach as proposed by Friede and Schmidli 2010. This review may result in an adjustment of sample size. Since this review will be performed in a blinded fashion, no adjustment for the type I error is needed. The blinded data review will be performed by AstraZeneca internal personnel or its designees and the full details of the review will be specified in a blinded data review plan.

Revised text:

The study will recruit subjects with blood eosinophil counts **<220/µL, 220-299/µL, and ≥300/µL**. **The approximately** 2:1 ratio **between ≥220/µL and <220/µL allows analysis of the primary** population for subjects most likely to respond to benralizumab **(i.e. ≥220/µL)**, while still including subjects below this threshold in order to help understand efficacy and safety in this group. The study is powered for the exacerbation rate comparisons of the subjects with blood eosinophils **≥220/µL** (primary efficacy analysis).

For the primary endpoint annual COPD exacerbation rate, 348 subjects with baseline blood eosinophil counts **≥220/µL** per treatment arm (1392 total) will need to be randomised to achieve 90% power of detecting a 30% reduction in both the 30mg and 100mg benralizumab dose groups versus placebo based on a Hochberg Procedure (Hochberg 1988). This calculation has assumed two-sided 4% alpha level tests, an annual placebo rate of 0.93 events/subject (1.0 events/subject/56 weeks), a negative binomial shape parameter of 0.4, and a dropout rate of 10%. The sample size calculation is based on simulations and has accounted for the power loss from a proposed futility analysis (section 8.5.6).

As stated previously **an approximately** 2:1 ratio will be used for subjects with blood eosinophil counts **≥220/µL and <220/µL**. Therefore this study will randomise 174 subjects/arm (696 total) with baseline blood eosinophil counts **<220/µL**. **An additional 20 subjects/arm will also be recruited to the 220-299/µL cohort to better characterize patients within this cohort. This addition results in 368 subjects/arm in the ≥220/µL cohort (1472 total). A total of 2168 subjects are expected to be randomised in this study. Details of the estimated numbers of recruited subjects/arm in each cohort (<220/µL, 220-299/µL, ≥300/µL) are described in the SAP**.

The sample size necessary to achieve a stated power (90% in our case) in this study is calculated based on the estimate of overall exacerbation rate and shape parameter from the negative binomial model (section 8.5.1). In order to better estimate the overall exacerbation rate and shape parameter, we plan to conduct a single blinded sample size re-estimation in both studies D3251C0003 and D3251C0004. Blinded estimates of the overall exacerbation rate as well as the shape parameter from data pooled across placebo and all benralizumab doses (for patients with eosinophil counts **≥220/µL**) will be used in the sample size re-estimation and strictly no treatment information will be used in the review. The pooled study summaries will not contain any information that would potentially reveal the treatment assignments (e.g., post-randomization eosinophil levels). The review will be conducted before the last patient with eosinophil counts **≥220/µL** is randomized and after the futility analysis (section 8.5.6). The exacerbation rate and shape parameter will be estimated using the maximum likelihood approach as proposed by Friede and Schmidli 2010. This review may

result in an adjustment of sample size. Since this review will be performed in a blinded fashion, no adjustment for the type I error is needed. The blinded data review will be performed by AstraZeneca internal personnel or its designees and the full details of the review will be specified in a blinded data review plan.

Reason for Amendment:

This change reflects 1) the accommodation of the new blood eosinophil boundary of ≥220/µL for the primary analysis which was implemented in order to better identify an eosinophil threshold for predicted response to Benralizumab, and 2) The additional recruitment of 20 subjects/arm in the 220-299/µL cohort in order to better characterize patients within this cohort.

Persons who initiated the Amendment:

Redacted , Global Product Statistician Delegate

Section of protocol affected:

8.5   Methods for statistical analyses

Testing strategy to account for multiplicity considerations

Previous text:

To account for multiplicity to test the primary (exacerbation) and two key secondary endpoints (FEV1 and SGRQ) for each of the 30mg and 100mg dose groups (for subjects with baseline blood eosinophils ≥300/µL) a testing strategy will be followed to control the overall type I error rate at level 0.05.

Revised text:

To account for multiplicity to test the primary (exacerbation) and two key secondary endpoints (FEV1 and SGRQ) for each of the 30mg and 100mg dose groups (for subjects with baseline blood eosinophils **≥220/µL**) a testing strategy will be followed to control the overall type I error rate at level 0.05.

Reason for Amendment:

This change reflects the new eosinophil boundary of ≥220/µL.

Persons who initiated the Amendment:

Redacted , Global Product Statistician Delegate

Section of protocol affected:

8.5.1   Primary analysis method(s)

Previous text:

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

…

Exacerbation rate in each of the three benralizumab dose groups will be compared to exacerbation rate in the placebo group using a negative binomial model. The response variable in the model will be the number of COPD exacerbations over the 56-week treatment period. The model will include covariates of treatment group, country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and the number of exacerbations in the year before the study. The logarithm of the follow-up time will be used as an offset variable in the model.

…

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

Revised text:

The primary efficacy variable is the annual COPD exacerbation rate and the primary analysis is to compare the annual COPD exacerbation rate of each benralizumab dose group with placebo in subjects with baseline blood eosinophil counts **≥220/µL**.

…

Exacerbation rate in each of the three benralizumab dose groups will be compared to exacerbation rate in the placebo group using a negative binomial model. The response variable in the model will be the number of COPD exacerbations over the 56-week treatment period. The model will include covariates of treatment group, **eosinophil cohort (220-299/µL or ≥300/µL)**, country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and the number of exacerbations in the year before the study. The logarithm of the follow-up time will be used as an offset variable in the model.

…

In addition, the exacerbation rate will also be summarized in subjects with baseline blood eosinophil counts **<220/µL,** <150/µL, **150-219/µL, 220-299/µL,** 300-449/µL, and ≥450/µL separately for descriptive purpose only.

16(22)

Reason for Amendment:

This change reflects the new eosinophil boundary of ≥220/μL for the primary efficacy endpoint and the inclusion of an additional covariate – eosinophil cohort (220-299/μL or ≥300/μL) – in the statistical analysis model.

Persons who initiated the Amendment:

Redacted , Global Product Statistician Delegate

Section of protocol affected:

8.5.2.1 Analysis methods for secondary efficacy variables

Previous text:

All the secondary efficacy endpoints will be analyzed in subjects with baseline blood eosinophil counts ≥300/μL. In addition, the two key secondary endpoints will also be summarized in subjects with baseline blood eosinophil counts <300/μL, <150/μL, 150-299/μL, 300-449/μL, and ≥450/μL separately for descriptive purpose only.

Change from baseline in pre-dose/pre-bronchodilator FEV1 at Week 56 will be compared between each of the three benralizumab dose groups and placebo using a repeated measures analysis on subjects with a baseline pre-dose/pre-bronchodilator FEV1 and at least one post-randomisation pre-dose/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 country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), visit, the interaction between visit and treatment and baseline pre-bronchodilator FEV1 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 FEV1=Treatment group+ baseline FEV1+ country + background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA) + visit + treatment*visit

…

Proportion of subjects with ≥4-point decrease (improvement) in SGRQ total score at Week 56 in each of the two benralizumab dose groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for country and background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA). Cumulative distribution function of absolute changes in SGRQ total score at week 56 will be plotted in a figure.

The proportion of subjects with ≥1 COPD exacerbation during the 56 weeks of treatment will be addressed as a supportive variable to the primary objective. The proportion in each of the two benralizumab dose groups will be compared with the proportion in the placebo group using a logistic regression model with country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and number of exacerbations in the year before the study as covariates.

Time to first COPD exacerbation will be analyzed as another supportive efficacy variable to the primary objective to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment, country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and number of exacerbations in the year before the study.

…

The number of nights with awakening due to COPD and requiring rescue medication will be analyzed as the response variable by fitting an ANCOVA model to data. Treatment group will be fitted as the explanatory variable, and country, baseline value and background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA) will be fitted as covariates. Rescue medication use (average puffs/day) will be analyzed using a similar model.

Change from baseline in E-RS total score and domain scores at Week 56 will be analyzed separately using a similar model as the model for change from baseline in pre dose/prebronchodilator FEV1. AUC of E-RS total score will be analyzed by fitting an ANCOVA model with treatment, country, baseline value, and background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA) as covariates.

Revised text:

All the secondary efficacy endpoints will be analyzed in subjects with baseline blood eosinophil counts **≥220/µL**. In addition, the two key secondary endpoints will also be summarized in subjects with baseline blood eosinophil counts **<220/µL,** <150/µL, **150-219/µL, 220-299/µL**, 300-449/µL, and ≥450/µL separately for descriptive purpose only.

Change from baseline in pre-dose/pre-bronchodilator FEV1 at Week 56 will be compared between each of the **three** benralizumab dose groups and placebo using a repeated measures analysis on subjects with a baseline pre-dose/pre-bronchodilator FEV1 and at least one postrandomisation pre-dose/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 **eosinophil cohort (220-299/µL or ≥300/µL)**, country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), visit, the interaction between visit and treatment and baseline prebronchodilator FEV1 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 FEV1=Treatment group+ **eosinophil cohort (220-299/µL or ≥300/µL)** + baseline FEV1+ country + background therapy(ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA) + visit + treatment*visit*

…

Proportion of subjects with ≥4-point decrease (improvement) in SGRQ total score at Week 56 in each of the **three** benralizumab dose groups will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for **eosinophil cohort (220-299/µL or ≥300/µL)**, country, and background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA). Cumulative distribution function of absolute changes in SGRQ total score at week 56 will be plotted in a figure.

The proportion of subjects with ≥1 COPD exacerbation during the 56 weeks of treatment will be addressed as a supportive variable to the primary objective. The proportion in each of the **three** benralizumab dose groups will be compared with the proportion in the placebo group using a logistic regression model with **eosinophil cohort (220-299/µL or ≥300/µL)**, country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and number of exacerbations in the year before the study as covariates.

Time to first COPD exacerbation will be analyzed as another supportive efficacy variable to the primary objective to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment, **eosinophil cohort (220-299/µL or ≥300/µL)**, country, background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), and number of exacerbations in the year before the study.

…

The number of nights with awakening due to COPD and requiring rescue medication will be analyzed as the response variable by fitting a **repeated measures** model to data. Treatment group will be fitted as the explanatory variable, and **eosinophil cohort (220-299/µL or ≥300/µL)**, country, baseline value and background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA) will be fitted as covariates. Rescue medication use (average puffs/day) will be analyzed using a similar model.

Change from baseline in E-RS total score and domain scores at Week 56 will be analyzed separately using a similar model as the model for change from baseline in pre dose/prebronchodilator FEV1. AUC of E-RS total score will be analyzed by fitting an ANCOVA model with treatment, **eosinophil cohort (220-299/µL or ≥300/µL)**, country, baseline value, and background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA) as covariates.

Reason for Amendment:

This change reflects 1) the new eosinophil boundary of ≥220/μL for all secondary efficacy endpoints, 2) the inclusion of an additional covariate – eosinophil cohort (220-299/μL or ≥300/μL) – in the statistical analysis models, and 3) the update of ANCOVA analysis to repeated measures analysis for all continuous endpoint analyses across time (consistent with the SAP).

Persons who initiated the Amendment:

Redacted , Global Product Statistician Delegate

Section of protocol affected:

8.5.5   Subgroup analysis

Previous text:

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 for the following factors: background therapy (ICS/LABA, LABA/LAMA, or ICS/LABA/LAMA), gender, age, geographic region, BMI, history of exacerbations during the previous year, and race. Data will be analyzed by Negative Binomial regression similar to the primary analysis and the same output will be presented for each subgroup as for the primary analysis. For the statistical modelling 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 are performed on the full analysis set.

Revised text:

Details of all subgroup analyses and statistical modeling including possible testing of interaction between treatment group and covariates will be described in the SAP.

Reason for Amendment:

This change updates the subgroup analysis section to be detailed in the SAP.

Persons who initiated the Amendment:

Redacted , Global Product Statistician Delegate

Section of protocol affected:

8.5.6   Interim Analysis

Previous text:

The futility analysis will be based on the pooled data of study D3251C00003 and study D3251C00004 when approximately 15% patients in the ≥300/µLeosinophil stratum have completed the studies. The percentage of patients is based on the total number of patients expected to be recruited in the ≥300/µLeosinophil stratum of the studies. In the futility analysis, decision will be based on the comparison of the futility boundary and the estimated exacerbation rate reductions of benralizumab doses vs. placebo in patients with eosinophil counts ≥300/µLfrom the negative binomial model as documented for the final analysis in section 8.5.1. Futility will be declared if the higher exacerbation rate reduction of benralizumab 30mg vs. placebo and benralizumab 100mg vs. placebo is less than 8%. A futility boundary of 8% was chosen based on the operating characteristics of ~55% chance of stopping the study for futility under the null hypothesis of equal exacerbation rates across all treatments and ~2% chance of stopping the study for futility assuming an exacerbation rate reduction of 30% for both benralizumab doses vs. placebo.

Revised text:

The futility analysis will be based on the pooled data of Study D3251C00003 and Study D3251C00004 when approximately 15% subjects with baseline blood eosinophil counts **≥220/µL** have completed the studies. The percentage of patients is based on the total number of patients with eosinophil counts **≥220/µL** expected to be recruited in the studies. In the futility analysis, decision will be based on the comparison of the futility boundary and the estimated exacerbation rate reductions of benralizumab doses vs. placebo in patients with eosinophil counts **≥220/µL** from the negative binomial model as documented for the final analysis in section 8.5.1. Futility will be declared if the higher exacerbation rate reduction of benralizumab 30mg vs. placebo and benralizumab 100mg vs. placebo is less than 8%. A futility boundary of 8% was chosen based on the operating characteristics of ~55% chance of stopping the study for futility under the null hypothesis of equal exacerbation rates across all treatments and ~2% chance of stopping the study for futility assuming an exacerbation rate reduction of 30% for both benralizumab doses vs. placebo.

Reason for Amendment:

This change reflects the new eosinophil boundary of ≥220/µL.

Persons who initiated the Amendment:

Redacted   Global Product Statistician Delegate

Section of protocol affected:

LIST OF REFERENCES

Additional text:

Pascoe S et al 2015

Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord I, Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. Lancet Resp. Med. 2015; 3: 435-442.

Reason for Amendment:

Literature reference added to support the need to recruit a cohort with blood eosinophils ≥220/µL, which will now be considered the boundary of the primary analysis.

Persons who initiated the Amendment:

Redacted   Senior Director Inflammation Neuroscience and Respiratory