| | |
|---|---|
| **STATISTICAL ANALYSIS PLAN** | |
| **Study Code** | D3251C00014 |
| **Edition Number** | 3.0 |
| **Date** | 10-Dec-24 |

# A Multicenter, Randomized, Double-blind, Chronic-dosing, Parallel-group, Placebo-controlled Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab 100 mg in Patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) with a History of Frequent COPD Exacerbations and Elevated Peripheral Blood Eosinophils

Redacted for Public Disclosure

# TABLE OF CONTENTS

TABLE OF CONTENTS ..... 2
LIST OF TABLES ..... 6
LIST OF FIGURES ..... 7
LIST OF ABBREVIATIONS ..... 8
AMENDMENT HISTORY ..... 11
1 STUDY DETAILS ..... 15
1.1 Study objectives ..... 15
1.1.1 Primary objective ..... 15
1.1.2 Secondary objectives ..... 15
1.1.3 Safety objective ..... 16
1.1.4 Exploratory objectives ..... 16
1.2 Study design ..... 17
1.3 Number of patients ..... 19
1.4 Blinded sample size re-estimation ..... 19
2 ANALYSIS SETS ..... 20
2.1 Definition of analysis sets ..... 20
2.1.1 All patients analysis set ..... 20
2.1.2 Full analysis set (FAS) ..... 20
2.1.3 Safety analysis set ..... 20
2.1.4 Pharmacokinetic analysis set (PKS) ..... 21
2.2 Violations and deviations ..... 21
2.2.1 Important protocol deviations ..... 21
2.2.2 Presentation ..... 22
3 PRIMARY AND SECONDARY VARIABLES ..... 22
3.1 General definitions ..... 22
3.1.1 Visit window definitions ..... 22
3.1.2 Baseline definition ..... 25
3.1.3 Prior/concomitant medications ..... 26
3.2 Primary Endpoint ..... 26
3.3 Key Secondary Endpoints ..... 28
3.3.1 Annualized rate of severe COPD exacerbations ..... 28
3.3.2 St. George's Respiratory Questionnaire (SGRQ) ..... 29
3.3.3 Pre-bronchodilator $FEV_1$ (L) ..... 30
3.4 Secondary Endpoints ..... 30
3.4.1 Annualized rate of COPD exacerbations associated with an ER visit or hospitalization ..... 30
3.4.2 Proportion of patients with ≥1 COPD exacerbation ..... 31

3.4.3 Time to first COPD exacerbation (days) ..... 31
3.4.4 COPD Assessment Test (CAT) ..... 31
3.4.5 Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease (E-RS: COPD) ..... 32
3.4.6 Mortality rate ..... 32
3.4.7 Healthcare resource utilization due to COPD ..... 33
3.5 Safety outcome variables ..... 33
3.5.1 Adverse events ..... 34
3.5.2 Laboratory safety variables ..... 34
3.5.3 ECG ..... 35
3.5.4 Physical examination ..... 35
3.5.5 Vital signs ..... 36
3.6 Exploratory Endpoints ..... 36
3.6.1 Annualized rate of COPD symptom worsening events ..... 36
3.6.2 Total rescue medication use ..... 37
3.6.3 Exacerbations of Chronic Pulmonary Disease Tool – Patient-Reported Outcome (EXACT-PRO) ..... 37
3.6.4 Clinically Important Deterioration (CID) ..... 38
3.6.5 Patient perception of effect item from the Onset of Effect Questionnaire (OEQ) ..... 38
3.6.6 Dose and number of days on systemic corticosteroids ..... 39
3.6.7 European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) ..... 39
3.6.8 Peripheral blood eosinophil counts ..... 40
3.6.9 CCI ..... 40
3.6.10 CCI ..... 41
3.6.11 Pulmonary structure and function ..... 41
3.7 Pharmacokinetic variables ..... 42
3.8 Immunogenicity variables ..... 42
4 ANALYSIS METHODS ..... 43
4.1 General principles ..... 43
4.2 Testing strategy to account for multiplicity considerations ..... 44
4.3 Analysis methods ..... 46
4.3.1 Patient disposition ..... 46
4.3.2 Demographics and patient characteristics ..... 46
4.3.3 Prior and concomitant medications ..... 48
4.3.4 Study treatment administration ..... 48
4.3.5 Primary Endpoint ..... 49
4.3.5.1 Primary analysis ..... 49
4.3.5.2 Subgroup analysis for the primary outcome variable ..... 50
4.3.5.3 Supportive analysis for the primary outcome variable ..... 52
4.3.6 Key Secondary Endpoints ..... 52
4.3.6.1 Annualized rate of severe COPD exacerbations ..... 53
4.3.6.2 St. George's Respiratory Questionnaire (SGRQ) ..... 53

4.3.6.3 Pre-bronchodilator $FEV_1$(L) ..... 54
4.3.7 Secondary Endpoints ..... 55
4.3.7.1 Annualized rate of COPD exacerbations associated with an ER visit or hospitalization ..... 55
4.3.7.2 Proportion of patients with ≥1 COPD exacerbation ..... 55
4.3.7.3 Time to first COPD exacerbation ..... 55
4.3.7.4 COPD assessment tool (CAT) ..... 56
4.3.7.5 E-RS: COPD ..... 56
4.3.7.6 Mortality rate ..... 57
4.3.7.7 Healthcare resource utilization due to COPD ..... 57
4.3.8 Additional modelling for primary and key secondary endpoints ..... 57
4.3.9 Exploratory Endpoints ..... 57
4.3.9.1 Annualized rate of COPD symptom worsening events ..... 57
4.3.9.2 Total rescue medication use ..... 57
4.3.9.3 Exacerbations of Chronic Pulmonary Disease Tool – Patient-Reported Outcome (EXACT-PRO) ..... 58
4.3.9.4 Clinically Important Deterioration (CID) ..... 58
4.3.9.5 Patient perception of effect item from the Onset of Effect Questionnaire (OEQ) 58
4.3.9.6 Dose and number of days on systemic corticosteroids ..... 58
4.3.9.7 European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) ..... 58
4.3.9.8 Peripheral blood eosinophil counts ..... 58
4.3.9.9 Pulmonary structure and function ..... 59
4.3.10 Safety outcome variables ..... 60
4.3.10.1 Adverse events (AEs) ..... 60
4.3.10.2 Laboratory data ..... 62
4.3.10.3 ECGs ..... 62
4.3.10.4 Physical examination ..... 62
4.3.10.5 Vital signs ..... 62
4.3.11 Pharmacokinetic analyses ..... 63
4.3.12 Immunogenicity analyses ..... 63
5 INTERIM ANALYSES ..... 63
6 CHANGES OF ANALYSIS FROM PROTOCOL ..... 63
7 REFERENCES ..... 63
8 APPENDIX ..... 65
8.1 Accounting for missing data ..... 65
8.1.1 Multiple imputation methods ..... 65
8.1.1.1 Accounting for missing data for recurrent events (moderate or severe COPD exacerbation rate endpoint, severe COPD exacerbation rate endpoint) ..... 65
8.1.1.2 Accounting for missing data for continuous endpoints (pre-bronchodilator $FEV_1$ and SGRQ total score) ..... 73
8.1.2 Tipping point methods ..... 75
8.1.2.1 Exacerbation endpoints ..... 76
8.1.2.2 Continuous endpoints (pre-bronchodilator $FEV_1$ and SGRQ total score) ..... 76

8.2 Partial dates for adverse events and prior/concomitant medications ..... 78
8.3 Analysis plan for ADA data ..... 80
8.4 Efficacy estimands ..... 83
8.5 Inhaled Corticosteroids Dose Conversion ..... 88
8.6 Systemic Corticosteroids Dose Conversion ..... 88
8.7 CCI
8.7.1 CCI
8.7.2 CCI
8.7.3 CCI

# LIST OF TABLES

Table 1 Windows for assessments conducted every 4 weeks ..... 23
Table 2 Daily diary assessments ..... 23
Table 3 General windows for non-4-week assessments ..... 24
Table 4 Vital signs reference ranges ..... 36
Table 5 Characteristics and Categories for Subgroup Analysis of the Primary Endpoint ..... 50
Table 6 Treatment group used to perform imputations by Reason for withdrawal ..... 67
Table 7 Treatment arm used to perform imputations by reason for study treatment discontinuation ..... 71
Table 8 Summary of analysis ..... 73
Table 9 Overview of objectives and estimand attributes ..... 83
Table 10 Inhaled Corticosteroids Dose Conversion ..... 88
Table 11 Systemic Corticosteroids Dose Conversion ..... 89
Table 12 CCI [redacted] ..... 90
Table 13 CCI [redacted] ..... 90

# LIST OF FIGURES

Figure 1 Study design ..... 18
Figure 2 Multiple testing strategy for the primary and key secondary endpoints ..... 45

# LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| ADA | Anti-drug antibodies |
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| AZ | AstraZeneca |
| BD | Bronchodilator |
| BMI | Body Mass Index |
| BSA | Body Surface Area |
| CAT | COPD Assessment Tool |
| CFB | Change from baseline |
| CI | Confidence interval |
| CID | Clinically important deterioration |
| CMH | Cochran–Mantel–Haenszel |
| COPD | Chronic obstructive pulmonary disease |
| CCI | CCI |
| CTMS | Clinical Trial Management System |
| CSP | Clinical study protocol |
| CSR | Clinical study report |
| DB | Database |
| DBP | Diastolic blood pressure |
| DNA | Deoxyribonucleic acid |
| DRMI | Drop-out reason-based multiple imputation |
| ECG | Electrocardiogram |
| ECL | Electrochemiluminescent |
| eCRF | Electronic case report form |
| eDiary | Electronic diary |
| EOT | End of treatment |
| EQ-5D-5L | European quality of life-5 dimensions-5 levels |
| ePRO | Electronic patient-reported outcome |

| Abbreviation or special term | Explanation |
|---|---|
| ER | Emergency room |
| E-RS: COPD | Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease |
| EXACT-PRO | Exacerbations of Chronic Pulmonary Disease tool – Patient-reported Outcome |
| FAS | Full analysis set |
| $FEV_1$ | Forced expiratory volume in 1 second |
| FVC | Forced Vital Capacity |
| GGT | Gamma-glutamyltransferase |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| ICS | Inhaled corticosteroids |
| ICU | Intensive care unit |
| IgE | Immunoglobulin E |
| IM | Intramuscular |
| IP | Investigational product |
| IPD | important protocol deviations |
| ITT | Intent-to-treat |
| IV | Intravenous |
| IVRS | Interactive Voice Response System |
| LABA | Long-acting beta agonist |
| LAMA | Long-acting muscarinic antagonist |
| LLOQ | Lower limit of quantification |
| LSMEANS | Least squares means |
| MAR | Missing at random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed-effect model for repeated measures |
| N | Sample size |
| N/A | Not applicable |
| OFAS | Overall efficacy analysis population |
| OEQ | Onset of Effect Questionnaire |
| PFAS | Primary efficacy analysis population |
| PK | Pharmacokinetics |
| PN | Percent normal |
| PRO | Patient-reported outcome |
| PT | Preferred term |

| Abbreviation or special term | Explanation |
|---|---|
| Q1 | First quartile |
| Q3 | Third quartile |
| Q4W | Every four weeks |
| Q8W | Every eight weeks |
| qRT-PCR | Quantitative reverse-transcriptase polymerase chain reaction |
| RNA | Ribonucleic acid |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SBP | Systolic blood pressure |
| SC | Subcutaneous |
| SD | Standard deviation |
| SDG | Standardised Drug Grouping |
| SGRQ | St. George's Respiratory Questionnaire |
| SI | System international (units) |
| SOC | System organ class |
| $SpO_2$ | Oxygen saturation |
| TBL | Total bilirubin |
| ULN | Upper limit of normal |
| VCV | Veeva Clinical Vault |
| WHO DD | World Health Organization Drug Dictionary |
| WK | Week |

# AMENDMENT HISTORY

| Category*: Change refers to | Date | Description of change | In line with the CSP? | Rationale |
|---|---|---|---|---|
| Primary and key secondary endpoints | 18 October 2024 | • Add the efficacy estimands table to Appendix 8.4.<br>• Updates on the Multiple imputation methods in Appendix 8.1.<br>• Update the subgroup characteristics and categories for subgroup Analysis of the primary endpoint.<br>• Add high- dose ICS level at baseline to the subgroup analysis.<br>• Update the BMI categories for the subgroup analyses.<br>• Remove atopic status from the subgroup analysis.<br>• Update GOLD version to GOLD 2024.<br>• Update the definition of maximum follow-up time to time at risk for exacerbations.<br>• Added descriptions and statistical summary analyses on OFAS and PFAS.<br>• Add the cumulative mean number of moderate or severe exacerbation observed over 56 weeks figure to the primary endpoint. | N/A<br>(CSP version 1.0, 24APR2019) | Update and clarification. |
| Secondary endpoints | 18 October 2024 | • Clarification provided on mortality rate endpoint and adding the exposure-adjusted mortality rate.<br>• Clarification provided on the resources utilized for the | N/A<br>(CSP version 1.0, 24APR2019) | Update and clarification. |

| | | | | |
|---|---|---|---|---|
| | | endpoint Healthcare resource utilization due to COPD.<br>• Clarification on the data source collection for the endpoint Annualized rate of COPD exacerbations associated with an ER visit or hospitalization.<br>• Update the annualized rate of COPD symptom worsening events up to Week 56 instead of "through EOT".<br>• Clarification on the total rescue medication use and removing bi-weekly.<br>• Clarification on the CAT score.<br>• Clarification on the E.RS: COPD. | | |
| Safety endpoints | 18 October 2024 | • Update adverse events section, add the EAIR.<br>• Update AE with outcome of death to SAE with outcome of death<br>• Remove the liver function tests. | N/A<br>(CSP version 1.0, 24APR2019) | To align with the Updates in the safety guidance. |
| Exploratory endpoints | 18 October 2024 | • Update the analyses for the exploratory endpoints.<br>• Update the derivation rules for exploratory endpoint dose and number of days on systemic corticosteroids. The assessment of the endpoint is updated from "through 56" to "up to Week 56".<br>• Update the exploratory endpoint Clinically Important Deterioration (CID) endpoint. | N/A<br>(CSP version 1.0, 24APR2019) | • Update and clarification.<br>• To align with the Not required analyses for the CSR are added to the exploratory analysis plan (EAP)<br>• ADA titre result is reported as ≤50 in global population and ≤15 in mainland China population, then the titre should be imputed as 50 for global population |

| | | | | |
|---|---|---|---|---|
| | | • Add Appendix 8.7 for the CCI<br>• Clarification provided on summaries of baseline demographic data and patient characteristics by baseline eosinophil counts to align with the data sources Labcorop and Q2<br>• Updates on the ADA section and excluding the China assays from the presentations. | | titre summaries and 15 mainland China population titre summaries. |
| Other | 18 October 2024 | • Clarification to the IPD categories and the process for identifying and summarizing IPD<br>• Clarification to the definition of the analysis sets.<br>• Clarification to the Visit window tables.<br>• Clarification to the baseline definition.<br>• Add the definition of "on-treatment period" to general principles section for alignment.<br>• Add the statement on the spirometry assessments for the patients in PPD .<br>• Add statements to exclude the patients from sites impacted by CCI GCP CCI from the analyses.<br>• Add statements to exclude the patients from the PPD PPD GCP CCI | N/A<br>(CSP version 1.0, 24APR2019) | • To align with the guidance on the important deviation plan and protocol deviation plan.<br>• Update and clarification. |
| Appendices | 18 October 2024 | • Add "the control imputation" section for the continuous variables for the multiple imputation. | N/A<br>(CSP version 1.0, 24APR2019) | Update and clarification. |

| | | | | |
|---|---|---|---|---|
| | | • Replace the "on-treatment analyses" in the appendix to "sensitivity analysis under alternative estimands".<br>• Add the ICS conversion table.<br>• Add the systemic corticosteroids dose conversion.<br>• Clarification to Partial dates for adverse events and prior/concomitant medications. | | |
| Multiple Testing Procedure | 30 September 2019 | Update to multiple testing strategy to achieve strong control of Type I error. | No (CSP version 1.0, 24APR2019) | Based on regulatory review comments (FDA Correspondence dated 24 August 2019, Reference ID: 4482153). CSP text to be aligned with amended SAP for next CSP amendment. |
| Other | 30 September 2019 | Added tipping point sensitivity analysis for the primary and key secondary endpoints. | N/A (CSP version 1.0, 24APR2019) | Based on regulatory review comments (FDA Correspondence dated 24 August 2019, Reference ID: 4482153). |
| NA | 15 July 2019 | Initial version | | |

* Pre-specified categories are Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other.

# 1 STUDY DETAILS

This statistical analysis plan (SAP) outlines the analyses to be generated for the global clinical study report (CSR). Additional analyses required for regional submissions will be prespecified in a separate analysis plan and will be submitted to the appropriate authorities.

## 1.1 Study objectives

### 1.1.1 Primary objective

| Primary Objective | Endpoint/Variable |
|---|---|
| To evaluate the effect of benralizumab 100 mg on COPD exacerbations in patients with moderate to very severe COPD | Annualized rate of moderate or severe COPD exacerbations, where a COPD exacerbation is defined by symptomatic worsening of COPD requiring:<br>• 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<br>• Use of antibiotics; and/or<br>• An inpatient hospitalization or death due to COPD |

COPD chronic obstructive pulmonary disease.

### 1.1.2 Secondary objectives

| Secondary Objective | Endpoint/Variable |
|---|---|
| To evaluate the effect of benralizumab 100 mg on severe COPD exacerbations (leading to hospitalization or death) | Annualized rate of severe COPD exacerbations [a], where a severe COPD exacerbation is defined by symptomatic worsening of COPD requiring an inpatient hospitalization or results in death due to COPD |
| To evaluate the effect of benralizumab 100 mg on COPD exacerbations involving emergency room visits and hospitalizations | Annualized rate of COPD exacerbations that are associated with an emergency room/emergency department visit or a hospitalization due to COPD |
| To evaluate the effect of benralizumab 100 mg on other parameters associated with COPD exacerbations | Time to first COPD exacerbation |
| To evaluate the effect of benralizumab 100 mg on health status/health-related quality of life | • Change from baseline in SGRQ total [a]<br>• Change from baseline in SGRQ domain scores<br>• Change from baseline in CAT total score |
| To evaluate the effect of benralizumab 100 mg on respiratory symptoms | Change from baseline in E-RS:COPD total and domain scores |
| To evaluate the effect of benralizumab 100 mg on pulmonary function | Change from baseline in pre-dose/pre-bronchodilator $FEV_1$ at the study site [a] |

| Secondary Objective | Endpoint/Variable |
|---|---|
| To evaluate the effect of benralizumab 100 mg on all cause and respiratory-related mortality | Mortality rate |
| To evaluate the effect of benralizumab 100 mg on health care resource utilization due to COPD | Annualized rate of hospitalizations due to COPD; Length of hospital stay; ICU days; annualized rate of hospitalizations and emergency department visits combined due to COPD; annualized rate of unscheduled outpatient visits including unscheduled visits to study sites due to COPD; and annualized rate of unscheduled healthcare encounters due to COPD |
| To evaluate the pharmacokinetics and immunogenicity of benralizumab in this patient population | • Serum benralizumab concentration<br>• Anti-benralizumab antibodies |

[a] Key secondary efficacy endpoints

CAT COPD assessment tool; COPD chronic obstructive pulmonary disease; E-RS:COPD Evaluating Respiratory Symptoms in COPD; ICU intensive care unit; SGRQ St. George's Respiratory Questionnaire; $FEV_1$ Forced expiratory volume in 1 second.

### 1.1.3 Safety objective

| Safety Objective | Endpoint/Variable |
|---|---|
| To evaluate the safety and tolerability of benralizumab in patients with moderate to very severe COPD | Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory, and ECG.<br>Assessments related to AEs cover:<br>• Occurrence/frequency<br>• Relationship to IP as assessed by investigator<br>• Intensity<br>• Seriousness<br>• Death<br>• AEs leading to discontinuation of IP<br>• Other significant AEs |

AE adverse event; COPD chronic obstructive pulmonary disease; ECG electrocardiogram; IP investigational product.

### 1.1.4 Exploratory objectives

| Exploratory Objective | Endpoint/Variable |
|---|---|
| To evaluate the effect of benralizumab 100 mg on COPD symptom-related events requiring an increase in rescue medication | Annualized rate of COPD symptom worsening events, where an event is defined by symptomatic worsening and increase in rescue medication as recorded in the eDiary |
| To evaluate the effect of benralizumab 100 mg on rescue medication use | Total rescue medication use (average puffs/day) |

| | |
|---|---|
| To evaluate the effect of benralizumab 100 mg on the severity, frequency and duration of EXACT-PRO defined events | EXACT-PRO |
| To evaluate the effect of benralizumab 100mg on disease progression composite endpoints | Clinically Important Deteriorations (CID) |
| To evaluate the onset of effect of benralizumab 100 mg | Patient perception of effect item from the Onset of Effect Questionnaire (OEQ) |
| To evaluate the effect of benralizumab 100mg on systemic corticosteroid use | Reduction in dose and number of days on systemic corticosteroids |
| To evaluate the effect of benralizumab 100 mg on general health status | EQ-5D-5L |
| To evaluate the effect of benralizumab 100 mg on peripheral blood eosinophil levels | Peripheral blood eosinophil counts |
| To evaluate the effect of benralizumab 100 mg on serum biomarkers [a] | Serum protein biomarkers CCI |
| To collect and store CCI from a voluntary patient sample for exploratory CCI analyses [a] | A CCI sample for CCI will be collected from patients who have consented to participate in the exploratory CCI analyses component of the study |
| To evaluate the effect of benralizumab 100 mg on CCI CCI CCI CCI | Change from baseline in: CCI CCI CCI CCI CCI CCI CCI CCI |

[a] Results for this exploratory objective may be reported outside of this Clinical Study Report.
COPD chronic obstructive pulmonary disease; EQ-5D-5L European Quality of Life-5 Dimensions; EXACT-PRO Exacerbations of Chronic Pulmonary Disease Tool – Patient-reported Outcome; RNA ribonucleic acid.

## 1.2 Study design

This is a randomized, double-blind, placebo-controlled, parallel-group, multi-centre, Phase 3 study to evaluate the efficacy and safety of a benralizumab 100 mg dose administered by subcutaneous (SC) injection every 4 weeks for the first 3 doses and then every 8 weeks thereafter (hereafter referred to as Q8W) in patients with moderate to very severe COPD with a history of frequent COPD exacerbations and elevated peripheral blood eosinophils (≥300/µL). Eligible patients must have a history of ≥2 moderate and/or severe COPD exacerbations in the previous year despite receiving triple (ICS/LABA/LAMA) background therapy. Eligible patients must also have an elevated blood eosinophil count of ≥300/µL at screening supported by at least 1 historical result of ≥150/µL within the previous year.

Potentially eligible patients will enter the run-in period of 5 weeks (subject to extension, refer to CSP Section 4.1.2). Patients who meet eligibility criteria will be randomized in a 1:1 ratio to receive either benralizumab 100 mg or placebo Q8W. The treatment period will be of variable duration and will continue until the last patient has the opportunity to complete a minimum of 56 weeks, at which point all patients will complete the study; see CSP Section 4.1.3. The primary endpoint will be analysed at Week 56.

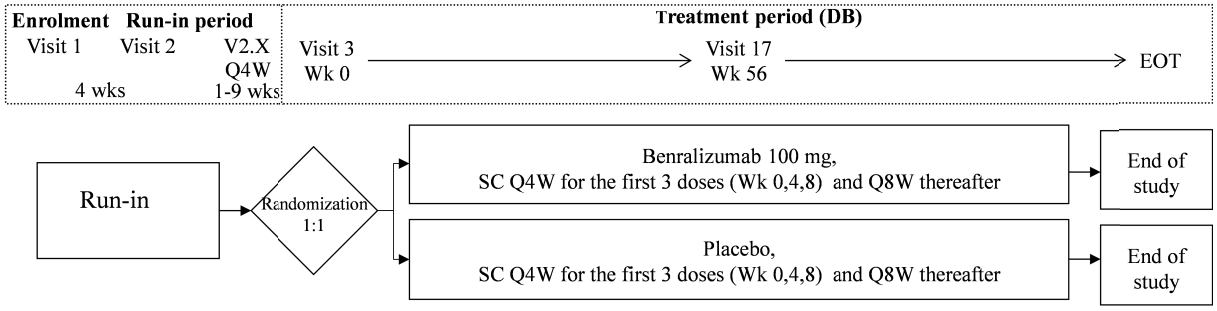
At randomization, patients will be stratified by country and number of exacerbations in the previous year (2 or ≥3). Randomization to the stratum of 2 exacerbations in the previous year will be capped to ensure ≥70% of patients with ≥3 exacerbations in the previous year in the study population.

Patients will be maintained on triple (ICS/LABA/LAMA) background therapy, from enrolment throughout the run-in and treatment periods. Background inhaled medications may be provided/reimbursed by AstraZeneca (also referred to as 'AZ' or sponsor), based on local regulations on patient participation in research studies and medication access.

This study will be conducted at approximately 400 sites in up to 30 countries.

The general study design is summarized in Figure 1. See CSP Section 1.1, Tables 1 and 2 for a detailed list of visits and assessments.

**Figure 1 Study design**




**Run-in Period:** The duration of run-in period is flexible and can be extended by up to 13 weeks (91 ±3 days) total, or longer, if necessary, see CSP Section 4.1.2. Additional screening visits (2.1, 2.2, etc) will be scheduled in case of extension.

**Week 56:** Primary endpoint (annualized moderate-to-severe exacerbation rate reduction) will be assessed over the first 56 weeks.

**End of Treatment (EOT) visit (end of study):** The treatment period will be of variable duration and will continue until the last patient has the opportunity to complete a minimum of 56 weeks. When the EOT visit has been identified for the last patient, then the final visits for all patients will be scheduled. The study will end when all patients complete their final visit.

DB double blind; Q4W every 4 weeks; Q8W every 8 weeks; SC subcutaneously; V Visit; Wk Week.

## 1.3 Number of patients

The study will recruit patients on triple (ICS/LABA/LAMA) background therapy with baseline eosinophil counts ≥300/μL and ≥2 exacerbations in the previous year, with at least 70% of patients with ≥3 exacerbations in the previous year. This study is powered for the primary population of patients with ≥3 exacerbations in the previous year.

For the primary endpoint of annualized exacerbation rate over the first 56 weeks, a minimum of 225 patients/arm with ≥3 exacerbations in the previous year (450 total) will be randomized to achieve approximately a 95% power to detect a 30% reduction in benralizumab 100 mg versus placebo. This calculation assumes a 2-sided 5% alpha level, an annualized placebo rate of 2, and a negative binomial dispersion parameter of 0.5. Assuming the same dispersion parameter, the trial retains approximately 90% power even if the assumed placebo rate drops to 1.4.

A total of 642 patients are expected to be randomized in the study, also including a cohort of patients with 2 exacerbations in the previous year to characterize efficacy in patients with ≥2 exacerbations in the previous year.

Power for severe exacerbations is heavily dependent on the assumed placebo rate, dispersion parameter and mean follow-up time, all of which may be impacted by the COVID-19 pandemic. With 642 patients and a 2-sided 5% significance level, assuming a negative binomial dispersion parameter of 2.7, and mean follow-up time of 2 years, and a placebo rate ranging from 0.12 to 0.24, power to detect a 40% reduction in severe exacerbation rate for benralizumab compared to placebo ranges from 63% to 80%.

## 1.4 Blinded sample size re-estimation

A blinded assessment of parameters relating to severe exacerbations might be conducted prior to the last patient's Week 56 visit. The blinded severe exacerbation rate, dispersion parameter, and the mean follow-up time at the time of study completion will be estimated, as well as the projected number of patients experiencing at least 1 severe exacerbation. The summaries will not contain any information that would potentially reveal treatment assignments (e.g. post-randomization eosinophil levels). If conducted, this analysis will not lead to any alteration of sample size and will not have any impact on any of the endpoints assessed over the first 56 weeks. However, the last patient last visit date may be extended to allow additional follow-up for severe exacerbations. 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 separate BSSR analysis plan.

# 2 ANALYSIS SETS

## 2.1 Definition of analysis sets

Four analysis sets are defined: All patients analysis set, full analysis set (FAS), safety analysis set, and pharmacokinetics (PK) analysis set.

Patients must have provided their informed consent. If no signed informed consent is collected, then the patient will be excluded from all analysis sets defined below. The patients from the PPD impacted by the CCI GCP CCI (non-compliance) and the patients impacted by PPD GCP CCI will be excluded from full analysis set, safety analysis set and PK analysis set.

### 2.1.1 All patients analysis set

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

### 2.1.2 Full analysis set (FAS)

All randomized patients who received at least 1 dose of investigational product (IP) and not impacted by CCI GCP CCI or PPD GCP CCI will be included in the full analysis set (FAS) irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat (ITT) principle. Patients who withdrew consent or assent to participate in the study will be included up to the date of their study termination.

Within the FAS, there is a primary efficacy analysis population of patients with ≥3 exacerbations in the previous year (abbreviated as PFAS elsewhere in this document). FAS is also referred to overall efficacy analysis population of patients with ≥2 exacerbations in the previous year (abbreviated as OFAS elsewhere in this document).

Unless otherwise noted, all secondary efficacy endpoints will be analysed in PFAS and repeated in OFAS using data up to Week 56.

All efficacy analyses will be performed using the FAS. For consistency, demographic and baseline characteristics will be presented using the FAS.

### 2.1.3 Safety analysis set

The safety analysis set consists of all patients who have received at least 1 dose of IP and not impacted by CCI GCP CCI or PPD GCP CCI Erroneously treated patients

(e.g., those randomised to treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they actually received. A patient who has received one or several occasions of benralizumab is classified in the benralizumab group.

All safety summaries and anti-drug antibodies (ADA) analyses will be based on the safety analysis set.

### 2.1.4 Pharmacokinetic analysis set (PKS)

All patients who received benralizumab and from whom pharmacokinetic (PKS) blood samples are assumed not to be affected by factors such as protocol violations (eg, disallowed medication) and who had at least 1 quantifiable serum PK observation post first dose and who were not impacted by CCI GCP CCI or PPD GCP CCI will be included in the PKS. All PK summaries will be based on this analysis set.

## 2.2 Violations and deviations

Patients who do not meet eligibility criteria but are still randomised and received at least 1 dose of IP will be analysed according to the analysis sets described in Section 2.1. There is no intention to perform a per-protocol analysis in this study.

### 2.2.1 Important protocol deviations

All protocol deviations identified during monitoring of the study will be recorded in the Veeva Clinical Vault (VCV) system, referred to as Clinical Trial Management System (CTMS). Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being.

The final list of important protocol deviations (IPD) will be documented prior to unblinding the study data. A detailed description on how IPDs will be collected and identified is referenced in the Protocol Deviation plan.

The IPDs will be grouped in the following general categories:

- Deviation 1: Inclusion Criteria Deviations
- Deviation 2: Exclusion Criteria Deviations
- Deviation 3: Discontinuation Criteria for IP met but participant not withdrawn from study treatment
- Deviation 4: Discontinuation Criteria for overall study withdrawal met but participant not withdrawn from study (Not Applicable)
- Deviation 5: Investigational Product Deviation

- Deviation 6: Excluded Medications Taken
- Deviation 7: Deviations Related to Study Procedure
- Deviation 8: Other Important Deviations

**Note:** Excluded Medications Taken are the prohibited medications as defined in the CSP Table 6.

Only important protocol deviations will be summarized and listed in the CSR. Potential important protocol deviations, both programmable or observable, will be reviewed quarterly at a minimum and at the time of blinded data reviews. Additional details, including key inclusion and exclusion criteria, are provided in the Non-Compliance Handling Plan.

### 2.2.2 Presentation

The number and percentage of participants meeting each IPD criterion will be summarized by treatment group and overall. Participants who deviate from a given criterion more than once will be counted once for that criterion. Any participants with more than one IPD will be counted once in the IPD category summary.

# 3 PRIMARY AND SECONDARY VARIABLES

## 3.1 General definitions

### 3.1.1 Visit window definitions

For the exacerbation-related analyses, no windows will be applied. For endpoints that present visit-based data, the variables will be summarized based on the scheduled days with adjusted analysis-defined visit windows. The adjusted analysis-defined visit windows will be based on the collection schedule listed in the protocol and variables will be windowed to the closest scheduled visit for that variable.

Visit windows have been constructed so that every observation collected can be allocated to a particular visit, including unscheduled assessments. No visit windows will be defined for screening visits.

The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls halfway between the two visits (the lower limit of the first post-baseline visit will be Day 2).

The general adjusted analysis-defined visit windows for assessments conducted every 4 weeks are summarised in Table 1.

**Table 1 Windows for assessments conducted every 4 weeks**

| Analysis-Defined Windows Visit | Scheduled Study Day | Maximum Windows |
|---|---|---|
| Week 0 Day 1 | 1 | Study Day=1 |
| Week X | X*7+1=a | (a-(a - b)/2) ≤ Study Days≤ ((c-a)/2+a)-1<br>Except for X=4 where window is 2≤ Study Days≤ ((c-a)/2+a)-1 |

a is the scheduled study day corresponding to the current scheduled assessment of Week X.

b is the scheduled study day corresponding to the preceding scheduled assessment of Week X.

c is the scheduled study day corresponding to the next scheduled assessment of Week X.

Knowing that b=a-4*7 days and c= a+4*7 days.

Study day will be defined as *(Date of assessment - date of randomisation) +1*

For the patient-reported questionnaires collected using an electronic handheld device (eDiary), the following rules will be applied:

- For daily diary assessments, monthly means up to Week 56 followed by bi-monthly means after Week 56 will be calculated using daily diary entries over 28-day and 56-day periods, respectively. For example, the Weeks 1-4 value will be the average of daily diary assessments from the evening of Study Day 1 through the evening of Study Day 29 and the Weeks 5-8 value will be the average of daily diary assessments from the evening of Study Day 30 through the evening of Study Day 57 (Table 2).

- If more than 14 daily measures (>50%) within a monthly period (or 28 daily measures within a bi-monthly period) are missing, then the mean for that period is set to missing.

**Table 2 Daily diary assessments**

| Reporting Period | First Study Day Included | Last Study Day Included |
|---|---|---|
| Weeks 1-4 | 2 | 29 |
| Weeks 5-8 | 30 | 57 |
| Weeks 9-12 | 58 | 85 |
| Weeks 13-16 | 86 | 113 |
| Weeks 17-20 | 114 | 141 |
| Weeks 21-24 | 142 | 169 |
| Weeks 25-28 | 170 | 197 |
| Weeks 29-32 | 198 | 225 |
| Weeks 33-36 | 226 | 253 |
| Weeks 37-40 | 254 | 281 |

| | | |
|---|---|---|
| Weeks 41-44 | 282 | 309 |
| Weeks 45-48 | 310 | 337 |
| Weeks 49-52 | 338 | 365 |
| Weeks 53-56 | 366 | 393 |
| **Post Week 56 (bi-monthly)** | | |
| Weeks 57-64 | 394 | 449 |
| Weeks 65-72 | 450 | 505 |
| Weeks 73-80 | 506 | 561 |
| Weeks 81-88 | 562 | 617 |
| Weeks 89-96 | 618 | 673 |
| Weeks 97-104 | 674 | 729 |

For assessments (excluding ePRO) conducted not on 4-weekly basis, the window for the visits following baseline will be constructed as shown in Table 3.

**Table 3 General windows for non-4-week assessments**

| Analysis-Defined Windows Visit | Scheduled Study Day | Maximum Windows |
|---|---|---|
| Week 0 Day 1 | 1 | Study Day=1 |
| Week X | X*7+1=a | 2≤ Study Days≤ ((b-a)/2+a)-1 |
| Week Y | Y*7+1=b | ((b-a)/2+a) ≤ Study Days≤ ((c-b)/2+b)-1 |
| Week Z | Z*7+1=c | ((c-b)/2+b≤ Study Days |

Study Day is defined as Date of assessment – Date of randomization + 1 for efficacy summaries, Date of assessment – Date of first dose + 1 for safety summaries. If (b-a) or (c-b) is odd number, then use (b-a+1) or (c-b+1), respectively.

For each analysis parameter, the windowing will be based on the protocol-specified schedule of events as defined in Tables 1 and 2 of the protocol. If multiple readings are recorded within a single visit window, the rules below will be applied.

- If there are 2 or more observations within the same visit window, then the non-missing observation closest to the scheduled visit will be used in the analysis.
- If 2 observations are equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis.
- If 2 observations are collected on the same day, then the non-missing observation with the earlier collection time will be included in the analysis.

If a visit window does not contain any observations, then the data will remain missing.

For pre-bronchodilator $FEV_1$ (L), the non-missing value with acceptable quality (acceptable or borderline quality grade) which is closest to the scheduled visit will be included in the analysis.

For overall analyses not based on any particular study visit (e.g., maximum post-baseline value), all data will be listed and/or analysed, including any repeat or unscheduled visits, unless otherwise specified. For safety endpoints, all post-baseline results will be included in these overall analyses, up to and including the end of treatment (EOT) visit.

### 3.1.2 Baseline definition

In general, the last recorded value on or prior to the date of randomization will serve as the baseline measurement for efficacy endpoints while the last recorded value prior to first dose of study treatment will serve as the baseline measurement for safety endpoints. When time of assessment is not recorded or missing, it is assumed that assessments recorded on the date of first dose of study treatment were performed prior to dosing, except in cases of protocol-specified post-dose assessments. If there is no value prior to randomization (or the first dose of study treatment, depending on the endpoint), then the baseline value will not be imputed and will be set to missing.

- For categorical baseline respiratory disease characteristics captured directly in the eCRF (e.g. captured as yes or no), if 'yes' is indicated in any visit during enrolment (scheduled or unscheduled), 'yes' will be used.

- For pre-bronchodilator $FEV_1$ (L), the last non-missing value with acceptable quality (acceptable or borderline quality grade) on or prior to the date of randomization will be used as baseline. The first dose of study treatment is scheduled to be administered on the date of randomization, however if the first dose of study treatment is delayed until after the date of randomization, the last recorded value with acceptable quality prior to first dose of study treatment will be used as baseline measurement for spirometry parameters. For post-bronchodilator $FEV_1$, the highest value with acceptable quality from the same date as the pre-bronchodilator $FEV_1$ result will be used.

- For E-RS: COPD, data collected in the last 14 days prior to randomization will be used to calculate the individual E-RS: COPD total and subscale baseline means. If more than 7 daily measures/scores (>50%) are missing, then baseline is set to missing.

- For blood eosinophil count, all data summaries, and analyses by baseline blood eosinophil count category (>overall median, ≤overall median) or by continuous baseline blood eosinophil count (i.e., modeling activities), the last non-missing assessment prior to first dose of study treatment will be used as baseline.

### 3.1.3 Prior/concomitant medications

Background COPD medication (i.e., triple therapy) will be classified as a 'COPD medication at baseline' if it started on or prior to randomization and ongoing after randomization.

A medication will be regarded as prior if it was stopped on or before the date of randomization (medication stop date ≤ date of randomization).

A medication will be regarded as 'concomitant' if the start date is after the date of randomization, or if it started on or prior to the date of randomization and ongoing after the date of randomization.

## 3.2 Primary Endpoint

The annualized rate of moderate or severe COPD exacerbations over 56 weeks will be used as the primary efficacy variable.

A COPD exacerbation will be defined as a worsening in the patient's usual COPD symptoms that is beyond normal day-to-day variation, is acute in onset, lasts 2 or more days (or 1 single day if the worsening is so rapid and profound that the treating physician judges that intensification of treatment cannot be delayed), 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.
- Use of antibiotics
- An inpatient hospitalization due to COPD (defined as an inpatient admission ≥24 hours in the hospital, an observation area, the emergency department or other equivalent healthcare facility depending on the country and healthcare system)
- Results in death

The worsening/onset of symptoms must include at least 1 major COPD symptom and at least 1 other major or minor symptom from the list below:

- Major COPD symptoms: dyspnea, sputum volume, and sputum color
- Minor COPD symptoms: cough, wheeze, sore throat, cold symptoms (rhinorrhea or nasal congestion), and fever without other cause

All protocol-defined COPD exacerbations must fulfil the symptom criteria as noted above and be supported by an eDiary alert, with symptoms recorded on eCRF or an investigator justification. Most COPD exacerbations are associated with worsening of the symptoms described above. Clinical presentations may, however, vary among patients and it may not be possible to capture the symptoms (e.g. patient intubated upon arrival to the emergency department). If a subject's symptoms and the overall clinical findings support the diagnosis of a COPD exacerbation, but the symptomatic worsening does not meet criteria above, the investigator must justify the decision for defining the event as an exacerbation and document the reasoning in the eCRF. All COPD exacerbations recorded in the eCRF, including investigator justified exacerbations, will be included in analyses provided they are not within 7 days of a prior exacerbation as defined below.

An exacerbation will be considered **moderate** if it requires treatment with systemic corticosteroids and/or antibiotics and does not result in hospitalization or death. An exacerbation will be considered **severe** if it results in hospitalization or death.

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. A single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids. The corresponding stop date for this treatment will consequently be determined as the date of administration plus 2 days.

A COPD exacerbation that occurs ≤7 days of the last dose of systemic steroids (oral, intramuscular (IM), intravenous (IV)), last dose of antibiotics, or hospital discharge for a prior COPD exacerbation will be counted as the same exacerbation event for analysis, with the severity (moderate or severe) of the combined event set to the maximum severity of the two events. Inpatient hospitalization due to COPD occurring during an exacerbation should not be regarded as a new exacerbation. To be counted as a new exacerbation it must be preceded by at least 7 days in which none of the exacerbation criterion is fulfilled.

Maximum time at risk for calculation of the annualized COPD exacerbation rate is 56 weeks, defined as the time from randomization up to and including Week 56 regardless of whether the patient discontinues IP prior to Week 56. For a patient who discontinues the study or is lost to follow-up before Week 56, the follow-up time will be defined as the time from randomization to the time point after which an exacerbation could not be assessed.

Exacerbations that start after Week 56 will not be included in the primary analysis of the primary endpoint (see Section 4.3.5.1). If an exacerbation is ongoing at Week 56, the exacerbation will be counted in the calculation of annualized exacerbation rate, however the

maximum time at risk will be truncated at Week 56, as will the duration of the exacerbation in summary tables of the primary endpoint.

The number of days a patient experiences a COPD exacerbation, including the subsequent 7 days (when a further exacerbation would not be considered as a second exacerbation), will be subtracted from the maximum time at risk defined above. For example, if a subject has a single exacerbation which lasts 4 days, then 7+4=11 days will be subtracted from the maximum time at risk.

In the primary analysis, the number of exacerbations observed for a patient over 56 weeks will be used as the response variable. To get the summary statistics, the annualized exacerbation rate in each treatment group will be calculated using the time-based approach below:

*Annualized Exacerbation Rate = 365.25*Total Number of Exacerbations / Total time at risk within the treatment group (days)*

The annualized rate of moderate or severe COPD exacerbations up to Week 56 will also be calculated for OFAS and is included in the multiple testing strategy defined in Section 4.2.

The annualized rate of moderate or severe COPD exacerbations through EOT will be calculated as a supportive analysis for PFAS and OFAS, respectively. The total time at risk through EOT for calculation of the annualized rate is defined in Section 3.3.1. The on-treatment annualized exacerbation rate will be calculated similarly, as a sensitivity analysis, using only exacerbations and follow-up occurring during the on-treatment period.

The annualized rate of moderate or severe COPD exacerbations up to Week 56 will be calculated excluding any exacerbations treated with antibiotics alone, as a sensitivity analysis.

## 3.3 Key Secondary Endpoints

All key secondary efficacy endpoints will be analysed in PFAS and repeated in OFAS.

Where serially measured endpoints (e.g. SGRQ total score and $FEV_1$) are also collected beyond Week 56, additional models like those fitted on the data up to Week 56 will be used to assess these endpoints through EOT.

### 3.3.1 Annualized rate of severe COPD exacerbations

The annualized rate of severe COPD exacerbations (leading to hospitalization or death) through EOT is a key secondary endpoint included in the multiple testing strategy. It will be calculated similarly to the primary efficacy endpoint described in Section 3.2.

Maximum time at risk for calculation of the annualized severe exacerbation rate through EOT is variable and defined as the time from randomization up to and including the date of the EOT visit, which is scheduled 8 weeks after the last dose of IP. For patients who discontinue study treatment and remain in the study after the IP discontinuation visit, exacerbations will be counted from the time of randomization up to and including the date of their last study visit, including on-site or phone visits. For a patient lost to follow-up before EOT, the follow-up time will be defined as the time from randomization to the time point after which an exacerbation could not be assessed. If an exacerbation is ongoing at the EOT visit (or last study visit for patients who discontinued the study), the exacerbation will be counted in the calculation of annualized exacerbation rate, however the maximum time at risk will be truncated at the date of the EOT visit (or last study visit), as will the duration of the exacerbation.

The number of days a patient experiences a severe COPD exacerbation, including the subsequent 7 days (when a further exacerbation would not be considered as a second exacerbation), will be subtracted from the maximum time at risk defined above. For example, if a subject has a single exacerbation which lasts 4 days, then 7+4=11 days will be subtracted from the maximum time at risk.

The annualized rate of severe COPD exacerbations up to Week 56 will also be calculated in both the PFAS and OFAS, respectively, as a supportive analysis. The maximum time at risk up to Week 56 for calculation of the annualized rate is as defined in Section 3.2.

The on-treatment annualized severe exacerbation rate will be calculated similarly, as a sensitivity analysis, using only exacerbations and follow-up occurring during the on-treatment period through EOT as defined in Section 4.1.

### 3.3.2 St. George's Respiratory Questionnaire (SGRQ)

The change from baseline in SGRQ total score up to Week 56 is a key secondary efficacy endpoint and is included in the multiple testing strategy.

The SGRQ is a 50-item PRO instrument developed to measure the health status of patients with airway obstruction diseases (Evidera, Inc. 2014;Jones et al. 1991). The questionnaire is divided into 2 parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; and 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 3 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 et al. 2009).

The symptoms domain score will be set to missing if there are >2 missing items; activity domain score will be set to missing if there are >4 missing items; impacts domain score will be set to missing if there are >6 missing items; and total score will be set to missing if one of the 3 domain scores is missing.

Potential health status treatment benefits of benralizumab will be evaluated by comparing the change from baseline at Week 56 in SGRQ total score.

A 4-point threshold will be used to define the response. If SGRQ total score at Week 56 has a ≥4-point decrease from baseline, it is defined as "improvement"; if it has a ≥4-point increase, it is defined as "worsening". If the SGRQ total score change at Week 56 is not more than 4-points, it will be defined as "no change". Missing SGRQ total score change at Week 56 will be considered as "not evaluable".
For the responder analysis of SGRQ, a responder will be defined as an individual who had "improvement" at Week 56 (i.e., ≥4-point decrease in SGRQ total score at Week 56). Patients who had SGRQ total score change defined as "no change" or "worsening" will be considered as non-responders. If SGRQ total score change at Week 56 is not evaluable due to missing data, then the patient will also be treated as non-responder.

### 3.3.3 Pre-bronchodilator $FEV_1$ (L)

Pre-bronchodilator $FEV_1$ (L) change from baseline at Week 56 is a key secondary efficacy endpoint included in the multiple testing strategy.

Details regarding the definition of baseline for pre-bronchodilator $FEV_1$ is provided in Section 3.1.2. The change from baseline to each of the post-randomization visits up to EOT will be used as a supportive efficacy variable.

## 3.4 Secondary Endpoints

All secondary efficacy endpoints will be analysed in PFAS and repeated in OFAS.

### 3.4.1 Annualized rate of COPD exacerbations associated with an ER visit or hospitalization

The annualized rate of COPD exacerbations that are associated with an emergency room/emergency department (ER) or a hospitalization due to COPD through EOT will be calculated similarly to the primary efficacy endpoint described in Section 3.2. The time at risk for calculation of the annualized rate is as defined in Section 3.3.1. The emergence

room/emergence department (ER) and hospitalization due to COPD exacerbation are collected in COPDEX eCRF.

### 3.4.2 Proportion of patients with ≥1 COPD exacerbation

The proportion of patients with ≥1 moderate or severe exacerbation up to Week 56 will be used as a supportive variable to the primary outcome variable.

A moderate or severe exacerbation event will be defined in the same way as outlined in Section 3.2. In the statistical analysis, a binary variable taking on the value 1 if a patient has experienced 1 or more exacerbations up to 56 weeks and 0 otherwise will be used as the response variable.

### 3.4.3 Time to first COPD exacerbation (days)

Time from randomization to the first moderate or severe COPD exacerbation up to Week 56 will be a supportive variable to the primary outcome variable, and is calculated as follows:

$$\textit{Start Date of first COPD exacerbation} - \textit{Date of Randomization} + 1$$

An exacerbation event will be defined in the same way as outlined in Section 3.2. The time to first moderate or severe COPD exacerbation for patients who do not experience a moderate or severe COPD exacerbation up to Week 56 will be censored at Week 56, and for patients who discontinue or are lost-to-follow-up prior to Week 56, at the last time point after which an exacerbation could not be assessed.

Time from randomization to first severe COPD exacerbation through EOT will be derived using the same approach. The time to first severe COPD exacerbation for patients who do not experience a severe COPD exacerbation will be censored at the date of their EOT visit, and for patients who discontinue from study or are lost to follow up, at the last time point after which an exacerbation could not be assessed.

### 3.4.4 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 6-point response scales, which are defined by contrasting objectives 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. The CAT total score is the sum of all item responses. Scores range from 0 to 40 with higher scores indicative of greater COPD impact on health status. A score cannot be calculated if >2 responses are missing; when one or two items are missing, their scores can be set to the average of the non-missing item scores.

### 3.4.5 Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease (E-RS: COPD)

The E-RS: COPD 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: COPD is a subset of items from the EXACT-PRO. The E-RS: COPD was designed to be captured as part of the daily EXACT-PRO assessment. Summation of E-RS: COPD 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: 0–12) by summing the responses of items within a respective domain. As with the total score, higher domain scores indicate greater severity.

Individual daily E-RS: COPD total and subscale scores will be calculated and summarized as bi-weekly means.

The bi-weekly mean is calculated as the sum of all non-missing daily measures/scores over 14 sequential days divided by the number of non-missing daily measures/scores. If more than 7 daily measures/scores (>50%) within that period are missing, then the mean daily measure/score for that period is set to missing.

### 3.4.6 Mortality rate

The number and percentage of patients who die from any cause through EOT will be calculated along with the exposure-adjusted mortality rate. The number, percentage of respiratory related deaths with exposure-adjusted mortality rate will also be calculated. Respiratory related causes of death are summarised based on the SOC = Respiratory, thoracic and mediastinal disorders.

The exposure-adjusted mortality rate will be calculated for each treatment group.

The exposure adjusted mortality rate per 100 participant-years at risk will be calculated as:

$$\frac{number\ of\ patients\ who\ died}{total\ number\ of\ days\ at\ risk\ for\ death} \times 365.25 \times 100.$$

The total number of days at risk for death is defined as the sum across patients' time at risk for the death. Time at risk is the duration from the first IP dose to the death date for patient who died, or to the last visit date for patient who are alive.

### 3.4.7 Healthcare resource utilization due to COPD

COPD related healthcare resource utilization information will be collected by the Investigator/authorized delegate at each visit as specified in the protocol and recorded in the HEVENT eCRF module.

The following resources utilized through EOT will be presented:

- Annualized rate of hospitalizations (hospital admission or emergency department > 24 hours) due to COPD
- Length of hospital stay (hospitalization general care stays)
- ICU days (hospitalization intensive care stays)
- Annualized rate of hospitalizations and emergency department visits (emergency room visits/emergency department visits that lasted less than 24 hours) combined due to COPD
- Annualized rate of unscheduled outpatient visits (specialist, primary health care physician, other health care, home visit physician, home visit other health care) including unscheduled visits to study sites due to COPD
- Annualized rate of unscheduled healthcare encounters (phone call to physician, nurse, and other physician/healthcare provider) due to COPD

The annualized rate of each resource through EOT will be calculated similarly to the primary efficacy endpoint described in Section 3.2. Each healthcare resource utilization will be counted as individual event in the calculation, i.e., event occurs ≤7 days of the last event will be counted as a new event. The maximum follow-up time is used for calculation of the annualized rate is as defined in Section 3.3.1.

## 3.5 Safety outcome variables

The following safety data will be collected: reported AEs (including serious AEs), clinical chemistry, haematology, urinalysis, 12-lead electrocardiogram (ECG), physical examination and vital signs, including oxygen saturation.

All safety measurements will use all available data for analyses, including data from unscheduled visits and repeated measurements.

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

No safety data will be imputed. The handling of partial/missing dates for AEs and prior/concomitant medications is detailed in Appendix 8.2. Duration of AEs and prior/concomitant medications will not be calculated using imputed dates and will instead be set to missing.

### 3.5.1 Adverse events

Adverse events experienced by the patients will be collected throughout the entire study and will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) per the Data Management Plan.

Adverse events with an onset date on or after first dose of IP is considered treatment emergent.

AEs occurring during screening are AEs with a date of onset ≥ date of first screening visit and < date of the first dose of IP. AEs occurring during screening will only be listed.

If an AE has a missing onset date, then unless the stop date of the AE indicates otherwise, this will be considered a treatment emergent AE. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered a treatment emergent AE.

Adverse events that have missing causality or intensity (after data querying) should be left as missing. Guidance on missing safety data and imputation rules for partial or missing dates is detailed in Appendix 8.2.

### 3.5.2 Laboratory safety variables

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times detailed in the CSP. The parameters outlined in Section 8.2.1, Table 7 of the CSP will be collected.

In summaries, figures, and listings, lab results and normal ranges will be presented in System International (SI) units. Eosinophils absolute counts data from Labcorp will be presented in both SI and conventional units (cells/μL) in summaries.

For the purposes of clinical chemistry, haematology, and urinalysis shift tables, baseline will be defined as the last available non-missing assessment prior to first dose of randomized

treatment, and maximum or minimum value post-baseline will be calculated over the entire post-baseline period.

Changes in haematology and clinical chemistry variables between baseline and each post-baseline assessment will be calculated. The change from baseline is defined as the post-baseline visit value minus the baseline visit value. There will be no imputation for missing values. For values recorded with a leading greater than or less than ('>', '<') symbol, the reported numeric value will be used for analysis and the value with the symbol will be included in the listings, unless otherwise specified. For example, a value of <0.01 will be analysed as 0.01 and listed as <0.01.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). The central reference ranges will be used for laboratory variables. All absolute values falling outside the reference ranges will be flagged.

Urinalysis data will be categorized as negative (0), positive (+), or strongly positive (++, +++, or >+++) at each timepoint.

### 3.5.3 ECG

Single 12-lead electrocardiogram (ECG) measurements will be obtained in accordance with the protocol, with the baseline visit being defined as the last available non-missing measurement prior to first dose of randomized treatment (Visit 3).

The outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF by the Investigator/authorized delegate, with any abnormalities being recorded as not clinically significant or clinically significant.

The ECG results will also be transferred to a central reader.

### 3.5.4 Physical examination

Complete and brief physical examinations will be performed at time points specified in Tables 1 and 2 of the CSP. What is included in the assessment will be dependent on whether the examination is complete or brief, as described in Section 8.2.3 of the CSP. Only information on whether the assessment was performed or not is to be recorded. Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE.

### 3.5.5 Vital signs

Pre-dose vital signs (pulse, systolic blood pressure, diastolic blood pressure, respiratory rate, oral temperature and oxygen saturation [$SpO_2$]) will be assessed in accordance with the visit schedule provided in the CSP.

Changes in vital signs variables between baseline and each subsequent scheduled assessment will be calculated. Baseline is defined as the last value prior to the first dose of randomized treatment. The change from baseline is defined as the post-baseline visit value minus the baseline visit value. There will be no imputation for missing values.

Absolute values will be compared to the reference ranges in Table 4 and classified as low (below range), normal (within range or on limits) or high (above range). All values falling outside the reference ranges will be flagged.

**Table 4 Vital signs reference ranges**

| Parameter | Standard Units | Lower Limit | Upper Limit |
|---|---|---|---|
| Diastolic Blood Pressure (DBP) | mmHg | 60 | 120 |
| Systolic Blood Pressure (SBP) | mmHg | 90 | 160 |
| Pulse Rate | Beats/min | 40 | 120 |
| Respiratory Rate | Breaths/min | 8 | 28 |
| Body Temperature | Celsius | 36.5 | 38 |
| Oxygen saturation | % | 95 | 100 |

## 3.6 Exploratory Endpoints

### 3.6.1 Annualized rate of COPD symptom worsening events

The annualized rate of COPD symptom worsening events will be derived similarly to the annualized rate of moderate or severe exacerbations as defined in Section 3.2. COPD symptom worsening events are derived based on data recorded in the e-diary and must meet all the following criteria:

- Symptom worsening on at least 1 major and 1 minor symptom, or at least 2 major symptoms on at least two consecutive days
- Increase in rescue medication use by >4 puffs/day in total use compared to baseline on at least two consecutive days
- Event must be during the on-treatment period

- Event must be at least 7 days from the end of the previous event. (Note: events less than 7 days apart will be counted as one event)

Major COPD symptoms include dyspnoea, sputum volume, and sputum colour. Minor COPD symptoms include cough, wheeze, sore throat, cold symptoms (rhinorrhoea or nasal congestion), and fever without other cause.

The annualized rate of COPD symptom worsening events up to Week 56 be calculated.

### 3.6.2 Total rescue medication use

The number of rescue medication inhalations and nebulizer treatments taken will be recorded by the patient in the eDiary once daily in the evening.

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. The number of rescue medication inhalations and nebulizer treatments captured in the eDiary each day will be calculated per patient. One instance of nebulizer use is converted to 2 puffs.

Total rescue medication use (inhaler and/or nebulizer), defined as the number of puffs per day will be calculated as follows:

*Number of inhaler puffs + 2 x (number of nebulizer times)*

### 3.6.3 Exacerbations of Chronic Pulmonary Disease Tool – Patient-Reported Outcome (EXACT-PRO)

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 2008;Leidy et al. 2011). The instrument was developed for daily, at home, administration using a handheld electronic device. Respondents are instructed to complete the electronic diary (eDiary) each evening just prior to bedtime and to answer the questions while considering their experiences “today”, up to Week 56. 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 number, average duration, and severity of EXACT-PRO defined events will be evaluated.

EXACT-PRO daily total 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.

For EXACT-PRO, the baseline total score will be the mean score within patient over the 7 days prior to randomization. A minimum of 4 days of data (>50%) is required for calculating the baseline total score. To allow for improvement or deterioration in disease state over the course of the trial, baseline total score will 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. An increase in EXACT-PRO total score ≥9 for 3 days or ≥12 for 2 days indicate an event has occurred. Calculating event duration requires identification of the following 5 parameters: 1) onset; 2) 3-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 (Jones et al. 2011;Leidy et al 2008;Leidy et al. 2011)

To produce summary statistics, the annualized EXACT-PRO defined exacerbation rates up to Week 56 in each treatment group will be calculated using the same time-based approach as specified in Section 3.2.

### 3.6.4 Clinically Important Deterioration (CID)

Clinically Important Deterioration (CID) is a composite endpoint assessing three important aspects (lung function, health status, and exacerbations) of worsening in COPD (Singh et al. 2016). CID is defined as having met at least one of the following criteria up to Week 56:

- ≥100 mL decrease in pre-bronchodilator $FEV_1$ compared to baseline,
- Decline in health-related quality of life (≥4 unit increase in SGRQ total score compared to baseline),
- ≥1 moderate or severe on-treatment COPD exacerbation.

### 3.6.5 Patient perception of effect item from the Onset of Effect Questionnaire (OEQ)

The Onset of Effect Questionnaire (OEQ) is an assessment of patient-perceived medication effects with a 1-week recall period (Leidy et al 2008).

The patients will complete only OEQ item 1: “During the past week, you could tell that your study medication was working.” Response options are ‘*strongly agree’*, ‘*somewhat agree’*, ‘*neither agree nor disagree’*, ‘*somewhat disagree’*, and ‘*strongly disagree’*. This item will be completed on the eDiary 7±2 days after each scheduled visit for IP administration up to Week 48.

Patients will be considered as responders if they answer 'strongly agree' or 'somewhat agree' to OEQ item 1 after the Week 48 IP administration.

Patients who answer, '*neither agree nor disagree'*, '*somewhat disagree'* or '*strongly disagree'* will be considered as non-responders. If the OEQ item 1 is not evaluable due to missing data, then the patient will also be treated as a non-responder.

### 3.6.6 Dose and number of days on systemic corticosteroids

All systemic corticosteroids will be converted to a prednisone equivalent dose using the conversion factors in Appendix 8.6.

The total number of days patient was treated with systemic corticosteroids due to COPD exacerbation from randomisation up to Week 56 will be derived for each patient based on information collected in the concomitant medication module of the eCRF.

For each patient, cumulative total dose up to Week 56 will be calculated by summing the systemic corticosteroids doses from day 1 until Week 56 (including). The cumulative total dose will be standardized by the observed time (in days) before Week 56 and multiplied by the expected time up to Week 56 (in days) using the following formula:

*Standardized cumulative total dose = [Cumulative total dose/observed time before Week 56] * expected time up to Week 56*

The expected time up to Week 56 for patients who complete Week 56 will be the observed time before Week 56. The expected time up to Week 56 for patients who early withdraw from study before Week 56 will be 392 days.

For each patient, average daily systemic corticosteroids dose up to Week 56 will be derived as follows:

*Average daily systemic corticosteroids dose = Cumulative total dose / Total number of days treated with systemic corticosteroids*

A single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids. Therefore, a single depot injection will count as 3 days of treatment with systemic corticosteroids for the purpose of calculating the average daily systemic corticosteroids dose.

### 3.6.7 European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L)

The EQ-5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options ('*no*

*problems*', '*slight problems'*, '*moderate problems'*, '*severe problems'*, and '*extreme problems'*) that reflect increasing levels of difficulty.

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

The questionnaire will be completed by the patients using the ePRO device every 4 weeks for the first 56 weeks and every 24 weeks thereafter.

### 3.6.8 Peripheral blood eosinophil counts

Absolute peripheral blood eosinophil count assessed by a central laboratory as a part of safety haematology testing according to the visit schedule defined in CSP Table 1Table 1 and CSP Table 2. Two central laboratories, Labcorp and $Q^2$, are used in study for haematology testing.

An important marker of the biological activity of benralizumab is the reduction in eosinophils in the peripheral blood. Absolute eosinophil counts along with their absolute changes from baseline, and percent changes from baseline for each post-baseline visit will be calculated using conventional units (cells/µL).

The data from Labcorp and $Q^2$ laboratories will be summarised and analysed separately.

### 3.6.9 CCI [redacted] biomarkers and CCI [redacted]

CCI [redacted] samples for exploratory analysis will be collected prior to IP administration for all patients, in accordance with the schedule provided in Table 1 of the CSP.

Analysis will be performed on biomarkers thought to play a role in CCI [redacted], including but not limited to CCI [redacted] The intended purpose is to evaluate the association of these biomarkers with observed clinical responses over the entire treatment duration of the clinical study and to enhance knowledge of COPD pathogenesis.

CCI [redacted] is the study of the transcriptome, the complete set of RNA transcripts that are produced by the CCI [redacted]. These include, but are not limited to CCI [redacted] analysis will be performed on CCI [redacted] isolated from CCI [redacted] blood CCI [redacted] samples.

Exploratory biomarker samples will not be collected in China. Results from the exploratory biomarker analyses will be reported separately from the CSR.

### 3.6.10 CCI sampling

CCI isolation will be collected at one time point only from patients who have consented to participate in the CCI component of the study.

Samples can be collected at any time after the CCI form is signed. The blood sample should be collected at randomization (Week 0); however, it may be taken at any visit until the last study visit. In the event of CCI, a replacement CCI sample may be requested from the patient.

Results for this exploratory endpoint analysis will be reported outside of the CSR.

### 3.6.11 CCI

CCI

CCI

- CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI CCI

CCI

CCI

## 3.7 Pharmacokinetic variables

Blood samples (processed to serum) for pharmacokinetic assessments will be collected from all patients at baseline prior to first benralizumab administration at Week 0 Day 1 and at post-baseline visits before benralizumab administrations during the treatment period in accordance with the visit schedule provided in Tables 1 and 2 of the CSP.

Serum concentrations of benralizumab will be determined using a validated electrochemiluminescent (ECL) immunoassay.

Serum concentrations that are <LLOQ will be reported as follows:

Individual concentrations below the LLOQ of the bioanalytical assay are non-quantifiable and will be reported as <LLOQ in the listings with the LLOQ defined in the footnotes of the relevant table and listing. Serum concentrations that are <LLOQ will be handled as follows for the provision of descriptive statistics:

- All <LLOQ values will be substituted with the value of zero, and all descriptive statistics will be calculated accordingly.
- If all concentrations are <LLOQ at a time point, no descriptive statistics will be calculated for that time point. The Geometric mean, Arithmetic mean, SD, min, Q1, median, Q3 and max will be reported as <LLOQ and the CV% as not calculated (NC).
- The number of <LLOQ values, n will be reported for each time point along with the total number of collected values (n).

## 3.8 Immunogenicity variables

Anti-drug antibody (ADA) results will be generated and analysed as per the details in Appendix 8.3.

# 4 ANALYSIS METHODS

## 4.1 General principles

- All efficacy endpoints will be analysed PFAS (patients with ≥3 exacerbation in the previous year) and repeated in OFAS (patients with ≥2 exacerbation in the previous year), where the number of exacerbations in the previous is as reported in the eCRF. Patients will be analysed according to their randomized treatment. Where serially measured endpoints (e.g. SGRQ and $FEV_1$) are also collected beyond Week 56, additional models similar to those fitted on the data up to Week 56 will be used to assess these endpoints over the longer follow-up period through EOT. Details regarding primary and key secondary estimands with additional details including sensitivity analyses are provided in Appendix 8.4.

- Safety endpoints will be assessed over the follow-up period through EOT.

- For all the statistical analysis, the stratification factors for the analysis will be using the IVRS data and the number of exacerbations in the previous year is from eCRF since IVRS doesn't collect the actual count of exacerbations in the previous year.

- Patients from PPD will be excluded from the analysis due to GCP CCI and CCI [redacted].

- Patients from the PPD impacted by the CCI [redacted] GCP CCI (non-compliance) will be excluded from the analysis.

- The analysis of safety endpoints will be based on the safety analysis set. Analysis sets are defined in Section 2.

- A treatment policy estimand will be applied to the primary analysis of the primary endpoint (along with the main analysis of key secondary endpoints) whereby all data up to Week 56 is included, regardless of whether a patient remains on blinded study treatment or not. The estimands and intercurrent event strategies for primary endpoint and key secondary endpoints are described in Appendix 8.4.

- On-treatment period: The on-treatment period starts on the date of randomization and ends on Week 56 or the last dose of IP + 56 days, whichever is earlier for endpoints analysed up to/at Week 56. It will be from the date of randomization to the date of last dose of IP + 56 days for endpoints analysed through EOT.

- Summary data will be presented in tabular format by treatment group. Categorical data will be summarized by the number and percentage of patients in each category. Continuous variables for parametric data will be summarized by descriptive statistics including N, mean, SD, median, minimum and maximum. All data will be listed. Data listings will be sorted by treatment and patient number.

- All hypothesis testing will be reported using 2-sided tests and all p-values will be nominal.

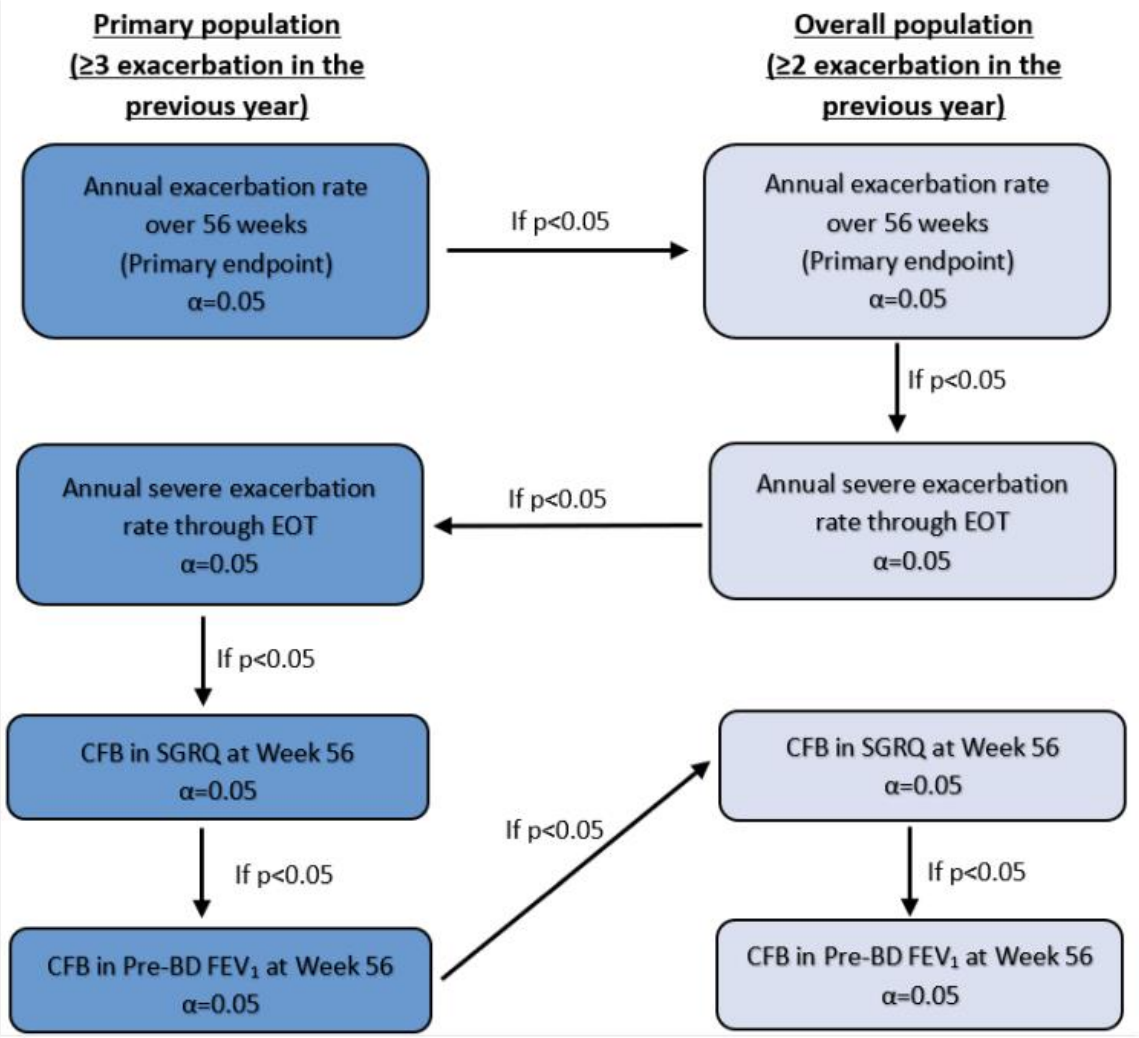
- The absolute change from baseline is computed as (*visit value – baseline value*). Percent change from baseline is computed as *((visit value – baseline value)/baseline value)* × 100%. If either a visit value or the baseline value is missing, the absolute change from baseline value and the percent change from baseline will also be set to missing.

- The data analyses will be conducted using the SAS® System (SAS Institute Inc., Cary, NC). All SAS® programs used to generate analytical results will be developed and validated according to AstraZeneca SAS® programming standards and validation procedures.

## 4.2 Testing strategy to account for multiplicity considerations

To account for multiplicity testing for the primary endpoint (annualized rate of moderate to severe COPD exacerbations) and 3 key secondary endpoints (severe exacerbations, SGRQ total score, and pre-bronchodilator $FEV_1$) in both PFAS (≥3 exacerbations in the previous year) and the OFAS (≥2 exacerbations in the previous year), a testing strategy will be used to strongly control the overall type I error rate at the 0.05 level. The testing strategy is depicted in Figure 2.

**Figure 2 Multiple testing strategy for the primary and key secondary endpoints**




BD bronchodilator; CFB change from baseline; EOT End of Treatment visit.

Note: testing within the hierarchy can only continue if the p-value is below the indicated threshold, and the treatment effect favours the benralizumab treatment arm.

If the null hypothesis for the primary endpoint in the primary population (see Section 4.3.5.1) is rejected, with a treatment effect in favour of benralizumab and p-value <0.05, testing will proceed for the primary endpoint in the overall population and for the key secondary endpoints in both primary and overall populations in a hierarchical order as illustrated in Figure **2**. Otherwise, no null hypotheses will be rejected for any other endpoint in either population.

Hierarchical testing will continue at the alpha level of 0.05 until a null hypothesis cannot be rejected; at this time, further testing will stop, and no subsequent null hypotheses in the testing hierarchy will be rejected.

## 4.3 Analysis methods

### 4.3.1 Patient disposition

Patient disposition will be summarized using the "all patients analysis set". The total number of patients will be summarized for the following groups: enrolled, enrolled excluding the sites impacted CCI GCP CCI and excluding PPD, and those who were not randomized (and reason). The number and percentage of patients within each treatment group will be presented by the following categories: randomized, randomized but excluded due to CCI GCP CCI or PPD GCP CCI randomized and not impacted by CCI GCP CCI or PPD GCP CCI received treatment with study drug, randomized but did not receive treatment with study drug (and reason). The percentage in disposition summary table will be calculated based on the number of patients randomized but not impacted by CCI GCP CCI or PPD GCP CCI

The following treatment and study status will be presented by treatment group: patients who received treatment, completed treatment up to Week 56, discontinued treatment before Week 56 but completed Week 56 of study, discontinued treatment by Week 56 and reasons, withdraw from study before Week 56. The above information will be presented for Week 104 and EOT, and separately for OFAS and PFAS, respectively.

Screen failure information will be listed for the "*all patients analysis set*".

The number of patients randomized by country and centre will also be summarized by treatment group for patients in OFAS and PFAS, separately.

The time to discontinuation of randomised treatment and withdrawal from the study will be presented using Kaplan Meier plots (overall and split by treatment related/not treatment related reason for discontinuation as presented in Appendix 8.1.1).

### 4.3.2 Demographics and patient characteristics

Demographics and baseline characteristics will be summarized by treatment group and for 'total' in the OFAS, using frequency and percentages (for categorical variables) and descriptive statistics of n, mean, standard deviation, minimum, Q1, median, Q3, and maximum (for continuous variables). If there are major differences between the FAS and safety analysis set, these summaries will also be repeated for the safety analysis set. Summaries will be repeated for patients in the PFAS.

Age will be derived from the date of informed consent and date of birth, rounded down to the nearest integer if full date of birth date is reported.

*Age (years)= ((date of informed consent – date of birth + 1)/365.25)*

If partial date of birth is reported with year, age will be calculated as (*year of informed consent – year of birth date*). For patients in countries where date of birth is not recorded, the age as recorded in the electronic case report form (eCRF) will be used.

Various baseline characteristics will also be summarized, including COPD background therapy, medical, surgical, and cardiovascular histories. Medical and surgical histories will be summarized by MedDRA PT within MedDRA SOC. Medical history will be summarized separately for past and current conditions. Specific medical and surgical histories, as well as significant radiological findings, will be summarized separately. The following will also be summarized for patients in the OFAS and repeated for PFAS:

- Subjects' characteristics (including but not limit to weight, height, BMI, ethnic group, baseline eosinophil count using Labcorp laboratory data, baseline eosinophil count using $Q^2$ laboratory data, historical eosinophil count). Historical eosinophil count will be used from eCRF form.

- Baseline pre-bronchodilator and post-bronchodilator lung function data ($FEV_1$ (L), $FEV_1$ (% PN), $FEV_1$/FVC), reversibility (%), and GOLD 2024 classification of severity of airflow limitation in COPD (Moderate: $FEV_1 \geq 50\%$ predicted but <80% predicted; Severe: $FEV_1 \geq 30\%$ predicted but <50% predicted; Very severe: $FEV_1$ <30% predicted).

- Respiratory disease characteristics (captured in the RESPHSMP eCRF form)

- Nicotine use and consumption (separately by smoking and smokeless nicotine products)

**Note:** For screening eosinophil, Q2 laboratory screening value will be used if it is >=300/uL. If Q2 laboratory result is not available or Q2 laboratory screening value is < 300/uL, then Labcorp screening value will be used. If multiple screening eosinophil values available from the same laboratory, the maximum of screening values will be used for summary.

Body mass index (BMI) is calculated as: $BMI\ (kg/m^2) = weight\ (kg)/(height\ (m))^2$.

### 4.3.3 Prior and concomitant medications

The number and percentage of patients taking maintenance COPD medications (i.e. Triple background therapy) at baseline will be summarized by treatment group and for 'total'.

Compliance with maintenance COPD medications will be summarized up to Week 56 and up to EOT by treatment group for the full analysis set, calculated as:

*100*(total days compliant/total days with completed data)*

A patient is considered compliant with maintenance COPD medication if they took their medication on that day as recorded in their daily diary.

The frequency and percentage of patients reporting usage of prior medications, concomitant medications will be summarized by treatment group and for 'total'. Medications will be categorized according to the WHO Drug Reference List dictionary which employs the Anatomical Therapeutic Chemical (ATC) classification system.

### 4.3.4 Study treatment administration

Duration of investigational product administration will be calculated in days as:

*Last dose date of IP - first dose date of IP + 1*

and will be summarized by treatment group for the safety analysis set. The number and percentage of patients with duration of IP administration in each of the following categories will also be summarized:

- ≤52 weeks (one year or less)
- >52 weeks and ≤104 weeks (between one and two years)
- >104 weeks and ≤156 weeks (between two and three years)
- >156 weeks (more than three years).

Study treatment compliance will be summarized by treatment group for the full analysis set and calculated as:

*Study treatment compliance = (total doses administered/total doses expected) * 100*

Patients who received no study treatment will have zero compliance. The total number of doses expected includes all visits with protocol scheduled IP administration on or before a patient's IP discontinuation or treatment completion date.

### 4.3.5 Primary Endpoint

#### 4.3.5.1 Primary analysis

The primary efficacy variable is the annualized rate of moderate or severe COPD exacerbations up to 56 weeks and the primary analysis is to compare the annualized COPD exacerbation rate of benralizumab with placebo in PFAS. Patients will be analysed according to randomized treatment.

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.,

$$H_0: \text{Rate ratio (benralizumab vs Placebo)} = 1$$

$$H_a: \text{Rate ratio (benralizumab vs Placebo)} \neq 1$$

The annualized COPD exacerbation rate in the benralizumab group will be compared to the annualized COPD exacerbation rate in the placebo group using a negative binomial model for the primary analysis. The response variable in the model will be the number of moderate or severe COPD exacerbations experienced by a patient up to Week 56. The model will include covariates of treatment group, region, and the number of exacerbations in the previous year. The logarithm of the patient's corresponding time at risk up to Week 56 will be used as an offset variable in the model to adjust for patients having different exposure times during which the events occur. If the model fails to converge, adjustment will be applied to the model and details will be added to the footnote of the corresponding outputs.

The annualized COPD exacerbation rate and the corresponding 95% confidence interval (CI) within each treatment group will be presented. The rate ratio of benralizumab versus placebo), corresponding 95% CI, and 2-sided p-values for the rate ratio will be presented. Marginal standardization methods will be used on the model estimates for all negative binomial analyses, unless otherwise specified.

The above negative binomial analysis will be repeated for the following:

- Patients with ≥2 exacerbations in the previous year.
- Patients with 2 exacerbations in the previous year (the number of exacerbations in the previous year will be excluded from covariate).

- On-treatment exacerbations in patients with ≥3 exacerbations in the previous year and in patients with ≥2 exacerbations in the previous year (i.e., include all available data up to Week 56 or the last dose of IP + 56 days, whichever is earlier), respectively.

- Excluding exacerbations treated with antibiotics alone in patients with ≥3 and ≥2 exacerbation in the previous, respectively.

Additional analyses to assess the robustness of the primary analysis results to missing data are outlined in Appendix 8.1.1 (multiple imputation methods) and in Appendix 8.1.2 (tipping point methods).

COPD exacerbation summary statistics will be presented based on the full analysis set by treatment group for patients in the primary and overall population. The individual exacerbation criteria (use of systemic corticosteroids, use of antibiotics, and inpatient hospitalization or death due to COPD) will also be summarized descriptively. The cumulative mean number of moderate or severe exacerbation observed over 56 weeks by treatment group will be presented in figure.

#### 4.3.5.2 Subgroup analysis for the primary outcome variable

To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analyses and statistical modelling including testing for interaction between treatment and covariates will be performed in PFAS for the characteristics listed in Table 5.

**Table 5 Characteristics and Categories for Subgroup Analysis of the Primary Endpoint**

| Baseline Subgroup | Subgroup Categories |
|---|---|
| Baseline blood eosinophils using Labcorp laboratory data | < overall median,<br>≥ overall median |
| Baseline blood eosinophils using $Q^2$ laboratory data | < overall median,<br>≥ overall median |
| Gender | Female,<br>Male |
| Age group categories | <65,<br>65-74,<br>≥75 years |
| Geographic region | Asia,<br>Eastern Europe,<br>Europe,<br>North America, |

| | |
|---|---|
| | Rest of world |
| BMI | <25,<br>25-30,<br>≥30 kg/m$^2$ |
| Race | White,<br>Asian,<br>Other |
| Smoking status | Current,<br>Former |
| High-dose ICS at baseline [1] | Yes,<br>No |
| Baseline GOLD classification of severity of airflow limitation in COPD [2] | Moderate,<br>Severe,<br>Very severe |
| Severe exacerbations during the previous year | No severe exacerbations,<br>≥1 severe exacerbation |
| CCI [redacted] | |
| Diagnosis of chronic bronchitis | Yes,<br>No |
| Diagnosis of emphysema | Yes,<br>No |

[1] If ICS result is ≥ 500 then High-Dose ICS = "Yes" else "High-Dose ICS" = "No" (Appendix 8.5).

[2] based on GOLD 2024.

CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]

CCI
CCI
CCI
CCI
CCI
CCI
CCI

For each of the subgroup factors, a separate negative binomial regression model will be fitted using the same model terms as used for the primary analysis (described in Section 4.3.5.1), with additional terms for the subgroup main effect and the treatment by subgroup interaction. Region is not a covariate if it is the subgroup.

Similar outputs will be presented for each subgroup as for the primary analysis. The p-value for the interaction term by each treatment group will be presented in the summary tables and forest plots.

It is important to note that the study has not been designed or powered to assess efficacy within any of these pre-defined subgroups, and as such these analyses are considered as exploratory.

#### 4.3.5.3 Supportive analysis for the primary outcome variable

As a supportive analysis, the annualized rate of moderate or severe COPD exacerbations through EOT in patients in the primary (PFAS) and overall population (OFAS) of patients, respectively will be analysed using the same method as described in Section 4.3.5.1.

Additionally, the annualized rate of moderate or severe COPD exacerbations through EOT for PFAS and OFAS will be summarized and analysed for the following follow-up intervals using the same method as described in Section 4.3.5.1:

- ≤52 weeks (one year or less)
- ≥52 weeks and <104 weeks (between one and two years)
- ≥104 weeks and <156 weeks (between two and three years)
- ≥156 weeks (more than three years).

### 4.3.6 Key Secondary Endpoints

All key secondary efficacy endpoints will be summarised and analysed separately in PFAS and OFAS.

For MMRM analyses over the entire EOT period, it may be required to truncate analyses to timepoints where sufficient patients are still being followed to allow for reliable model fitting. This decision will be made and documented following a blinded data review.

#### 4.3.6.1 Annualized rate of severe COPD exacerbations

Annualized rate of COPD exacerbations leading to hospitalization or death (i.e. severe exacerbations) will be analysed through EOT using a similar negative binomial model as outlined for the primary efficacy variable in Section 4.3.5.1 for patients in PFAS and OFAS, respectively.

If any notable differences in treatment effect are seen by subgroups for the primary endpoint of moderate or severe exacerbations, analyses of severe exacerbations in those subgroups may be conducted.

Additional analyses to assess the robustness of the results to missing data are outlined in Appendix 8.1.1 (multiple imputation methods) and in Appendix 8.1.2 (tipping point methods). As a supportive analysis, annualized rate of severe exacerbation will be analysed up tot Week 56.

#### 4.3.6.2 St. George's Respiratory Questionnaire (SGRQ)

Change from baseline in SGRQ total score at Week 56 is a key secondary endpoint and included in the multiple testing strategy.

Summary statistics for the score and change from baseline in SGRQ total score and the domain scores (symptoms, activity, and impacts) will be produced by treatment group and visit.

Change from baseline in SGRQ total score and the three domain scores (symptoms, activity, and impacts) up to Week 56 will be compared separately between the benralizumab group and placebo group using a mixed-effect model for repeated measures (MMRM) on patients in the PFAS and OFAS, respectively, who have baseline SGRQ assessment and at least one post-baseline SGRQ assessment.

Two separate MMRM analyses [assuming missing at random (MAR)] will be performed for SGRQ total score:

- The primary analysis under a treatment policy estimand will include all available data up to and including Week 56 (no data beyond Week 56 will be used) regardless of whether patients discontinue IP prematurely.

- The secondary analysis under an on-treatment estimand will include all available data up to Week 56 or the last dose of IP + 56 days, whichever is earlier.

The dependent variable will be the change from baseline in SGRQ score at post-baseline protocol-specified visits. Treatment group will be fitted as the explanatory variable, and region, visit, the interaction between visit and treatment, and baseline SGRQ score will be fitted as covariates. Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed in the following order: unstructured, Toeplitz, first-order autoregressive, compound symmetric, and variance components. If the procedure does not converge, the next covariance matrix will be used. Covariance parameters are estimated using the Restricted Maximum Likelihood method (REML) and denominator degrees of freedom will be estimated using the Kenward-Roger approximation. The model is:

*Change from baseline in SGRQ score = Treatment group + baseline SGRQ score + region + visit + treat*ment**visit.* Results will be presented in terms of least square means (LSMEANS), treatment differences in LSMEANS, 95% CI and p-values for all visits. The results at Week 56 will be of primary interest.

Line plot of SGRQ total score change from baseline over time up to Week 56 will be presented.

The proportion of subjects in terms of SGRQ total score response status (improvement, worsening, no change, and not evaluable) at Week 56 will be summarised descriptively by treatment group and visit. The proportion of subjects with ≥4-point decrease (improvement) in SGRQ total score at Week 56 in the benralizumab group will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel (CMH) test controlling for region. Patients with non-evaluable response status at Week 56 will be treated as non-responders. The results of the analyses will be presented as odds ratios with associated 95% CI and 2-sided p-value. The analysis will be repeated for patients in PFAS and OFAS, respectively.

Additional analyses to assess the robustness of the results in SGRQ total score to missing data are outlined in Appendix 8.1.1 (multiple imputation methods) and in Appendix 8.1.2 (tipping point methods). A supportive analysis will be conducted for change from baseline in SGRQ total score through EOT.

#### 4.3.6.3 Pre-bronchodilator $FEV_1$(L)

Change from baseline in pre-bronchodilator $FEV_1$ (L) at Week 56 is a key secondary endpoint and included in the multiple testing strategy.

Summary statistics of the change from baseline in pre-bronchodilator $FEV_1$ at the study site will be produced by treatment group and visit. Two separate MMRM analyses [assuming missing at random (MAR)] will be performed: The primary analysis under a treatment policy estimand will include all available data up to and including Week 56 (no data beyond Week 56 will be used) regardless of whether patients discontinue IP prematurely. The secondary analysis under an on-treatment estimand will include all available data up to Week 56 or the date of last IP dose + 56, whichever is earlier.

The above will be analysed using a similar model as for the change from baseline in SGRQ total score described in Section 4.3.6.2. Results will be presented in terms of LSMEANS, treatment differences in LSMEANS, 95% CI and p-values for all visits.

Additional analyses to assess the robustness of the MMRM analysis for pre-bronchodilator $FEV_1$ to missing data are outlined in Appendix 8.1.1 (multiple imputation methods) and 8.1.2 (tipping point methods). A supportive analysis will be conducted for change from baseline in pre-bronchodilator $FEV_1$ through EOT.

### 4.3.7 Secondary Endpoints

#### 4.3.7.1 Annualized rate of COPD exacerbations associated with an ER visit or hospitalization

Annualized rate of COPD exacerbations associated with an ER visit or hospitalization will be analysed through EOT using a similar negative binomial model as outlined for the primary efficacy variable in Section 4.3.5.1.

#### 4.3.7.2 Proportion of patients with ≥1 COPD exacerbation

The proportion of patients with ≥1 moderate or severe COPD exacerbation up to Week 56 will be addressed as a supportive variable to the primary objective. The proportion in the benralizumab group will be compared with the proportion in the placebo group using a logistic regression model with region and number of exacerbations in the previous year as covariates.

The results of the analyses will be presented using the odds ratio, together with associated 95% CI and 2-sided p-value. The number and percentage of patients with ≥1 COPD exacerbation will also be summarised by treatment group.

#### 4.3.7.3 Time to first COPD exacerbation

Time to first moderate or severe COPD exacerbation up to Week 56 will be analysed to explore the extent to which treatment with benralizumab delays the time to first moderate or severe exacerbation compared with placebo. A Cox proportional hazard model will be fitted to the data with the covariates of treatment, region, and number of exacerbations in the previous

year. Results will be summarised as hazard ratios, 95% CI and p-values (unstratified log-rank test). Time to first moderate or severe COPD exacerbation will also be displayed graphically using a Kaplan-Meier plot.

The percentage of patients who had a moderate or severe exacerbation at Week 26 and Week 56 will be estimated for each treatment group. These percentages will be estimated using the Kaplan-Meier technique.

These analyses will also be repeated for the time to first severe COPD exacerbation through EOT where severe exacerbations in the previous year (Yes, No) will be included as a covariate in the Cox proportional hazard model instead of number of exacerbations in the previous year.

#### 4.3.7.4 COPD assessment tool (CAT)

The CAT total scores, changes from baseline will be summarised by treatment group and visit. Change from baseline in CAT total score up to Week 56 will be analysed using a similar model as for the primary analysis of change from baseline in SGRQ total score described in Section 4.3.6.2 and replace SGRQ baseline by CAT baseline total score. Results will be presented in terms of LSMEANS, treatment differences in LSMEANS, 95% CI and p-values for all visits.

The number and percentage of patients with a ≥2-point decrease (improvement) in CAT total score (responder) will be summarised by treatment group at Week 56. Patients who have missing CAT total score at Week 56 will be considered as non-responders. The proportion of responders will be analysed using a CMH test controlling for region. The results of the analyses will be presented using odds ratio, together with associated 95% CI and 2-sided p-values.

#### 4.3.7.5 E-RS: COPD

The E-RS: COPD total scores and domain scores, and corresponding changes from baseline will be summarised by treatment group and visit.

Change from baseline in E-RS: COPD total score and domain scores up to Week 56 will be analysed separately using a similar MMRM model as for the primary analysis of change from baseline in SGRQ score described in Section 4.3.6.2 and replace baseline SGRQ by corresponding E-RS: COPD baseline score. Results will be presented in terms of LSMEANS, treatment differences in LSMEANS, 95% CI and p-values for all visits.

The number of percentage of patients with a ≥2-point decrease (improvement) in E-RS:COPD total score (responder) will be summarised by treatment group at Week 56. Patients with

missing E-RS:COPD total score at Week 56 will be considered as non-responders. The proportion of responders will be analysed using a CMH test controlling for region. The results of the analyses will be presented using odds ratio, together with associated 95% CI and 2-sided p-value.

#### 4.3.7.6 Mortality rate

The number and percentage of patients who die from any cause, along with the exposure-adjusted mortality rate will be presented by treatment group. Exposure-adjusted mortality rates will be derived as described in Section 4.3.10.1. Similar presentations will be produced for respiratory-related deaths.

If a sufficient number of events is observed during the study (to be confirmed in the SAP amendment prior to clinical data lock), a Cox proportional hazards model may be used to compare time to event for these mortality endpoints between treatment groups. Time to death will be displayed graphically using a Kaplan-Meier plot. For surviving patients, the time to death will be censored based on the last assessment date when the patient was confirmed as alive.

#### 4.3.7.7 Healthcare resource utilization due to COPD

The number and annualized rate of patients with COPD specific resource utilization during the treatment period will be summarised by treatment group.

### 4.3.8 Additional modelling for primary and key secondary endpoints

Additional sensitivity analyses may be conducted on the primary and key secondary endpoints to investigate the sensitivity of the efficacy conclusions upon removal of patient data from sites with data anomalies. The primary assessment of benefit-risk will be based on PFAS. Data anomalies may include but are not restricted to; sites with multiple benralizumab PK concentration level anomalies (e.g. patients with PK levels persistently below LLOQ or excessive PK concentrations); sites with high correlations in entry time of ePRO data; or sites with available ePRO data post-death.

### 4.3.9 Exploratory Endpoints

#### 4.3.9.1 Annualized rate of COPD symptom worsening events

Summary statistics of COPD symptom worsening event frequency and annualized rate will be produced by treatment group for OFAS and PFAS.

#### 4.3.9.2 Total rescue medication use

The total rescue medication use in puffs is the sum of the rescue medication patient took up to Week 56, regardless of treatment status. The average daily total rescue medication (puffs/day)

use will be derived as the total rescue medication use in puffs divided by the duration from date of randomization to Week 56. The summary statistics of average daily total rescue medication use (puffs/day) will be presented by treatment group.

#### 4.3.9.3 Exacerbations of Chronic Pulmonary Disease Tool – Patient-Reported Outcome (EXACT-PRO)

Summary statistics of the EXACT-PRO event frequency, duration, and severity will be produced by treatment group for PFAS and OFAS, respectively.

#### 4.3.9.4 Clinically Important Deterioration (CID)

Time to first CID (the first time when any of the components in CID is met) will be analysed using a Cox proportional hazard model with the covariates of treatment, region, and number of exacerbations in the previous year. Results will be summarised as hazard ratios, 95% CI and p-values (unstratified log-rank test). Patients who do not meet any of CID criteria up to Week 56 will be censored at Week 56, and for patients who discontinue or are lost-to-follow-up prior to Week 56, at the last study visit.

#### 4.3.9.5 Patient perception of effect item from the Onset of Effect Questionnaire (OEQ)

A summary of the number and percentage of patients in terms of OEQ response will be presented by treatment group and visit.

#### 4.3.9.6 Dose and number of days on systemic corticosteroids

Summary statistics for the number of days on systemic corticosteroids, standardized cumulative total dose, and average daily systemic corticosteroids dose due to COPD exacerbations will be provided up to Week 56.

#### 4.3.9.7 European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L)

The EQ-5D-5L responses from each dimension and the visual analog scale, and changes from baseline, will be summarised by treatment group and visit.

#### 4.3.9.8 Peripheral blood eosinophil counts

An important marker of the biological activity of benralizumab is the reduction in eosinophils in the peripheral blood. Eosinophil counts results from Labcorp laboratory will be used for the baseline and change from baseline calculations. The same analyses will be repeated for eosinophil counts from $Q^2$ laboratory.

Absolute eosinophil counts along with their absolute changes from baseline, and percent changes from baseline will be summarised by treatment group and visit using conventional units (cells/μL).

The eosinophil count will be log10-transformed first. When a result of 0 was recorded, a small value (i.e., half of minimum of non-missing positive value) is added prior to logarithm transformation. The change from baseline in log-transformed eosinophil counts up to Week 56 will be compared between the benralizumab group and the placebo group using a MMRM analysis, as defined for analysis of SGRQ total score in Section 4.3.6.2. The results will be transformed back to linear scale.

#### 4.3.9.9 CCI

CCI

CCI

- CCI
- CCI
- CCI
- CCI
- CCI
- CCI

CCI

- CCI
  - CCI
- CCI
  - CCI
  - CCI
  - CCI

CCI

CCI

CCI

CCI

CCI

CCI

### 4.3.10 Safety outcome variables

All safety variables will be summarised using the safety analysis set and data presented according to actual treatment received.

#### 4.3.10.1 Adverse events (AEs)

All AEs will be listed for each subject. All summaries will be presented for treatment emergent AEs by treatment group and will be exposure-adjusted to account for the variability in follow-up periods beyond 56 weeks, unless specify otherwise.

The exposure adjusted incidence rate (EAIR) (PHUSE 2017) of AEs per 100 participant-years at risk will be calculated as:

$$\frac{Number\ of\ patients\ reporting\ an\ AE}{Total\ number\ of\ days\ at\ risk\ for\ the\ AE} \times 365.25 \times 100$$

The total number of days at risk for an AE is defined as the sum across patients' time at risk for the AE. Time at risk is the duration from the first IP dose to the start date of the first AE for patient experiencing the AE, or to the last visit date for patient not experiencing the AE.

The incidence rates assumes that the treatment hazard is constant over the analysis period assessed. If this assumption is violated, the incidence rate could be considered as an average risk over the period assessed and thus may vary with the length of the observed period. An overall summary table will be produced showing the number, percentage, and EAIR of patients with at least 1 AE in any of the following categories: AEs, serious adverse events (SAEs), SAE with outcome of death, and AEs leading to discontinuation of investigational product (IP).

AEs, SAE with outcome of death, SAEs and AE leading to discontinuation of IP will be summarised by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by MedDRA. For each PT, the number, percentage and EAIR of patients reporting at least one occurrence will be presented (i.e., multiple occurrences of an AE for a patient will only be counted once).

A summary of the most common (frequency of >3%) AEs will be presented by PT. For each PT, the number, percentage and EAIR will be presented. A summary of non-serious AEs occurring in >5% of patients in any treatment group will be presented by PT. For each PT, the number and percentage will be presented.

Additionally, the EAIR, the difference in EAIR with 95% confidence interval between benralizumab and placebo will be generated for AEs, common AEs, SAEs, AEs leading to discontinuation of IP.

Related AEs and SAEs will be summarised by system organ class and preferred term presenting number, percentage, EAIR, and 95% CI. AE will be summarised by preferred term and maximum intensity. If a patient reports multiple occurrences of the same AE within the same study period, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe). No EAIR will be presented for AE by maximum intensity (mild, moderate, severe).

Adverse events of interest will include but may not be limited to helminth parasitic infection, injection site reactions, malignancy, and hypersensitivity events. Adverse events of helminth parasitic infection (high level group term of helminthic disorders), injection site reactions (high level term of injection site reactions), malignancy (standardized MedDRA query of malignant tumours) and hypersensitivity (standardized MedDRA query of hypersensitivity [narrow]) will be summarised by preferred term. The summary of injection site reactions will be summarised by injection site location and number of IP administrations. The EAIR and difference in EAIR with 95% confidence interval between benralizumab and placebo will be reported.

Plot of frequencies and risk differences (forest plots) between treatment arms will be presented for the most common adverse events, serious adverse events, adverse events causing discontinuation of investigational product and adverse events of interest including malignancy, injection sites reactions, helminth parasite infection and serious hypersensitivity.

Summaries of overall adverse events by category will be produced in the following subgroups.

- Age group (< 65, ≥65 years old)
- Gender (Male, Female)
- Race (White, Asian, Other)
- Geographic region (North America, rest of world, Japan)

The differences in EAIR (benralizumab – placebo) reporting at least 1 AE, at least 1 SAE with outcome of death, at least 1 SAE, and at least 1 AE leading to discontinuation of investigational product by the above subgroup, with associated 2-sided 95% confidence intervals using the Miettinen Nurminen (M-N) method will be constructed. The results from subgroup analysis will be presented in forest plots.

The key subject information tables will be generated for SAE, SAE with outcome of death, and adverse event leading to discontinuation of investigational product.

AEs reported in patients impacted by CCI [redacted] GCP CCI or PPD GCP CCI will be listed in a separate AE listing.

#### 4.3.10.2 Laboratory data

All protocol-specified continuous laboratory parameters will be summarised descriptively by absolute value at each visit by treatment group, together with the corresponding changes from baseline. All parameters will be summarised in SI units, except for blood eosinophil counts which will be summarised in both SI and conventional units. Results reported by the central laboratory in conventional units will be converted to SI units for reporting.

Central laboratory reference ranges will be used for the identification of abnormalities, and a shift table will be produced for each laboratory parameter to display low, normal, and high values. The shift tables will present baseline and maximum/minimum on-treatment value, as applicable for each parameter and will include patients with both baseline and post-baseline data.

Data for patients who have treatment-emergent changes outside central laboratory reference ranges will be presented.

For urinalysis data, a shift table will be generated to present changes from baseline to maximum post-baseline value for selected parameters and will include patients with both baseline and post-baseline data.

Any data outside the central laboratory reference ranges will be explicitly noted on the listings that are produced.

#### 4.3.10.3 ECGs

A shift table will be produced for ECG overall evaluation to display normal, abnormal – not clinically significant, abnormal – clinically significant, and not done. The shift tables will present baseline and last observation post-baseline value.

#### 4.3.10.4 Physical examination

Clinically significant physical exam findings will be reported as AEs and will be summarised as described in Section 4.3.10.1.

#### 4.3.10.5 Vital signs

Descriptive statistics and change from baseline for vital signs data will be presented for each treatment group by visit. Baseline to maximum post-baseline and baseline to minimum postbaseline value shift tables will be generated, as applicable for each parameter and will include patients with both baseline and post-baseline data.

### 4.3.11 Pharmacokinetic analyses

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

Benralizumab serum concentrations will be summarised using descriptive statistics at each visit by treatment group and will be listed in the CSR. The population modelling will be presented in a separate pharmacometrics report.

### 4.3.12 Immunogenicity analyses

Anti-drug antibody (ADA) assessments will be conducted and analysed as per the details in Appendix 8.3.

## 5 INTERIM ANALYSES

No interim analysis is planned. A blinded sample size re-estimation is described in Section 1.4.

## 6 CHANGES OF ANALYSIS FROM PROTOCOL

Not applicable.

## 7 REFERENCES

**Bafadhel et al 2011**
Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P, et al. Acute exacerbations of chronic obstructive pulmonary disease. Identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med. 2011;184:662–71.

**Barnard and Rubin. 1999**
Barnard J, Rubin DB. Small-sample degrees of freedom with multiple imputation. Biometrika 1999; 86:948-955.

**Stoel et al. 2008**
Stoel BC, Putter H, Bakker ME, Dirksen A, Stockley RA, Piitulainen E, Russi EW, Parr D, Shaker SB, Reiber JH, Stolk J. Volume correction in computed tomography densitometry for follow-up studies on pulmonary emphysema. Proc Am Thorac Soc 2008 Dec 15;5(9):919-24.

**Gottlow et al 2015**
Gottlow M, Hollis S, Wan R, Hirsch I, Darilay A, Weissfeld L, France L. A Simulation study of a controlled imputation approach for analyzing missing data in recurrent events due to early discontinuations. PSI Annual Conference 2015.

**Guideline on Missing Data 2010**
Guideline on Missing Data in Confirmatory Clinical Trials 2 July 2010 EMA/CPMP/EWP/1776/99 Rev.

**Evidera, Inc. 2014**
Evidera, Inc. The Exacerbations of Chronic Pulmonary Disease Tool (EXACT) Patient-Reported Outcome (PRO) USER MANUAL (Version 7.0).

**Jones et al. 1991**
Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med. 1991; 85 Suppl B:25-31.

**Jones et al. 2009**
Jones PW, Harding G, Berry P, Wiklund I, Chen W-H, Leidy NK. Development and first validation of the COPD Assessment Test. Eur Respir J 2009, 34: 648–654.

**Jones et al. 2011**
Jones PW, Chen WH, Wilcox TK, Sethi S, Leidy NK. Characterizing and quantifying the symptomatic features of COPD exacerbations. Chest 2011; 139(6):1388–1394.

**Keene et al. 2014**
Keene ON, Roger JH, Hartley BF, Kenward MG. Missing data sensitivity analysis for recurrent event data using controlled imputation. Pharmaceutical Statistics 2014, 13 258–264.

**Leidy et al 2008**
Leidy NK, Mathias SD, Parasuraman BM, Patrick DL, Pathak D. Development and validation of an onset of effect questionnaire for patients with asthma. Allergy Asthma Proc. 2008;29:590–9.

**Leidy et al. 2011**
Leidy NK, Wilcox TK, Jones PW, et al. Standardizing measurement of chronic obstructive pulmonary disease exacerbations. Reliability and validity of a patient-reported diary. Am J Respir Crit Care Med 2011; 183(3):323–329.

**Rubin 1987**
Rubin DB. Multiple imputation for nonresponse in surveys. 1987. New York: Wiley.

**Singh et al. 2016**
Singh D, Maleki-Yazdi MR, Tombs L, Iqbal A, Fahy WA, Naya I. Prevention of clinically important deteriorations in COPD with umeclidinium/vilanterol. Int J Chron Obstruct Pulmon Dis. 2016 Jun 24 ;11:1413-24. doi : 10.2147/COPD.S101612. PMID : 27445468; PMCID: PMC4928660.

**Sexton et al. 2010**
Sexton C, Notte S, Murray L, Leidy NK. PRO evidence dossier to support the use of the E-RS to evaluate respiratory symptoms in patients with COPD. United BioSource Corporation; Bethesda, MD: May 2010.

**Sexton et al. 2011**
Sexton C, Leidy NK, Notte SM, et al. Quantifying the severity of respiratory symptoms of COPD: reliability and validity of a patient diary. Poster presented at the American Thoracic Society International Meeting; May 2011: Denver, CO.

**Wan et al. 2015**
Wan R, Hirsch I, Gottlow M, Hollis S, Darilay A, Weissfeld L, France L. Controlled imputation approach for analyzing missing data in recurrent events due to early discontinuations. DIA/FDA Statistics Forum 2015.

# 8 APPENDIX

## 8.1 Accounting for missing data

### 8.1.1 Multiple imputation methods

#### 8.1.1.1 Accounting for missing data for recurrent events (moderate or severe COPD exacerbation rate endpoint, severe COPD exacerbation rate endpoint)

In this study some patients dropping out of the study potentially leads to unobserved events. The amount of missing data is minimized in this study as patients are encouraged to complete visits after they discontinue from randomised treatment.

This section summarizes how we will describe the pattern of and reasons for missing data from the study. It will also describe how we plan to account for missing data, including both the primary and sensitivity analyses to assess the robustness of the treatment effect under different underlying assumptions to account for missing data.

Multiple imputation methods will be performed for the primary and key secondary endpoints included in the multiple testing procedure if the primary endpoint in the primary population achieves statistical significance. If statistical significance is achieved, multiple imputation methods will also be performed for the primary endpoint in the overall population and each of the key secondary endpoints that achieve nominal statistical significance of 0.05.

##### 8.1.1.1.1 Missing data descriptions

Tabular summaries for the percentage of patients by the reason for discontinuation of randomised treatment as well as for withdrawal from the study will be presented by treatment to describe why patients discontinue from randomised treatment or withdraw from the study.

The time to discontinuation of randomised treatment and withdrawal from the study will be presented using Kaplan Meier plots (overall and split by treatment related/not treatment related reason for discontinuation, as defined in Table 6 and Table 7). Dependent on these outputs additional exploratory analyses may be produced as deemed necessary to further understand the pattern of missing data.

#### 8.1.1.1.2 Primary analysis under the Treatment Policy Estimand using the Missing at Random (MAR) assumption

The primary analysis for the primary endpoint of moderate or severe COPD exacerbations allows for differences in outcomes over the study treatment period up to 56 weeks to reflect the effect of initially assigned randomised treatment as well as if subsequent treatments are taken. This primary analysis includes all data until patients withdraw from the study or up to Week 56, whichever is earlier, regardless of if they discontinue from randomised treatment. The primary analysis uses the negative binomial regression model with (logarithm of) the time at risk as an offset term and assumes that missing data is missing at random (MAR) and is a direct likelihood approach (DL).

The primary analysis for key secondary endpoint of severe COPD exacerbations is as above, however uses data over the entire study treatment period through end of treatment (EOT).

#### 8.1.1.1.3 Sensitivity analyses under the Treatment Policy Estimand using both MAR and MNAR assumptions

To examine the sensitivity of the results of the primary analysis to departures from the underlying assumptions, additional analyses will be performed using controlled multiple imputation method introduced in Keene et al. 2014 and further developed to allow for different underlying assumptions to be used. As with the primary analysis the sensitivity analyses include all data until patients withdraw (up to Week 56 for the primary endpoint of moderate or severe COPD exacerbations and up to EOT for key secondary endpoint of severe COPD exacerbations) from the study regardless of if they discontinue from randomised treatment.

For this method an underlying negative binomial stochastic process for the rate of exacerbations is assumed and post study withdrawal counts will be imputed conditional upon the observed number of events prior to the withdrawal. This allows various assumptions about the missing data to be analysed by modifying the post-withdrawal model assumption. For the negative binomial model fit on data after imputation, the logarithm of the maximum follow-up time subtracting the time period when patient is experiencing observed exacerbation serves as an offset variable. However, the time period is not imputed for imputed exacerbation events. The maximum follow-up time for patients who early withdraw from study will be hypothetical Week 56 (392 days).

Imputation of post study withdrawal counts up to Week 56 will be performed for primary endpoint of moderate or severe COPD exacerbations and up to the EOT cut-off date (scheduled date of the last enrolled patient's EOT visit) for severe COPD exacerbations endpoint, given that the study uses a variable duration design for the period beyond Week 56. The final EOT cut-off date will be pre-specified in SAP amendment prior to clinical data lock.

The default assumptions that will be used to impute the missing data for patients who withdraw early from the study are as follows:

(a) **MAR:** Missing counts in each arm are imputed assuming the expected event rate within that arm.

(b) **Dropout Reason-based Multiple Imputation (DRMI):** Missing counts will be imputed differently depending on the reason for dropout; counts for patients in the benralizumab arm who dropped out for a treatment related reason are imputed based on the expected event rate in the placebo arm, whereas the remaining patients who have dropped out are imputed assuming MAR.

Some reasons for withdrawal are clearer to determine as treatment related (Adverse Events, Death) or non-treatment related (Subject lost to follow up,). Other reasons are less clear such as (severe non-compliance of protocol, withdrawal by subject and 'Other'), a review of each patient who withdraws from the study will therefore be carried out prior to unblinding the study. The review will include assessment of the reason for discontinuation of randomised treatment for those patients who discontinued randomised treatment and then withdrew from the study and also free text for when the reason for withdrawal or discontinuation of randomised treatment is recorded as subject decision or other. Based on this review the default assumptions for DRMI as described in b) and Table 6 may be changed. A list of these patients and the assumptions made under DRMI will be documented prior to unblinding of the study.

A summary of reasons for patients withdrawing from study and the corresponding treatment arm used to calculate the imputation exacerbation rate under MAR and DRMI is given in Table 6.

**Table 6 Treatment group used to perform imputations by Reason for withdrawal**

| Reason for withdrawal | MAR | DRMI |
|---|---|---|
| Development of study-specific withdrawal criteria* | NA | NA |
| Study terminated by sponsor | Benralizumab | Based on review prior to study unblinding |

| Reason for withdrawal | MAR | DRMI |
|---|---|---|
| Death | Benralizumab | Placebo |
| Adverse Event | Benralizumab | Placebo |
| Lost to follow-up | Benralizumab | Benralizumab |
| Physician decision | Benralizumab | Based on review prior to study unblinding |
| Site terminated by sponsor | Benralizumab | Based on review prior to study unblinding |
| Withdrawal by subject | Benralizumab | Based on review prior to study unblinding |
| Other | Benralizumab | Based on review prior to study unblinding |

Note: All patients on exacerbation rate in the placebo arm are imputed using the placebo arm rate.

*Development of study-specific discontinuation criteria is used only if patient withdraws due to closed stratum, thus not applicable for randomized patients.

Together with the primary analysis the sensitivity analyses are considered to cover the range from realistic to plausible worst-case assumptions about missing data. The MAR multiple imputation approach is expected to correspond closely to the primary analysis and is included to allow for comparisons with MNAR assumptions (specifically method b) using the same multiple imputation methodology.

The dropout reason-based multiple imputation (DRMI) approach was selected as the most conservative approach based on the fact that placebo patients are receiving standard of care and are not expected to change to a substantially more effective treatment after withdrawing from study or study treatment. For patients receiving benralizumab who withdraw from the study due to treatment related reasons it is assumed that at worst they would be on the standard of care treatment, i.e., the placebo arm. For patients receiving benralizumab who withdraw from the study due to non-treatment related reasons it seems reasonable to assume they would be similar to those patients who complete treatment.

The methodology used for sensitivity analysis is described in more detail in Keene et al. 2014. The steps for carrying out multiple imputation are outlined below.

**Step 1: Fitting a negative binomial model to the observed data**

A negative binomial regression model will be fitted to the observed exacerbation data with treatment group, region, and the number of exacerbations in the previous year included as covariates. The logarithm of the patient's corresponding time at risk up to Week 56 will be used as an offset variable in the model to adjust for patients having different exposure times during which the events occur.

**Step 2: Drawing samples from the posterior distribution**

The negative binomial distribution is conventionally defined as the probability distribution of the number of successes $Y$ before $k$ failures are seen in a series of independent Bernoulli trials with probability $p$ of success and $(1-p)$ of failure.

The posterior distribution for parameter $k$ and coefficients $\beta$ will be created as a product of non-informative prior and the likelihood from the model in Step 1. A uniform prior distribution will be assumed for the regression coefficients. A Gamma ($10^{-4}$, $10^{-4}$) will be assumed for $1/k$.

With the use of Markov Chain Monte Carlo (MCMC) method, 100 samples of $k$ and $\beta$ will be drawn from their posterior distribution. Convergence of the MCMC algorithm will be assessed.

A random seed of 482024 will be used. The first 2000 iterations will be discarded to allow for convergence to a stationary distribution and to remove the effect of the starting values ("burnin").

A gap of 100 iterations will be used between imputations to ensure independence between imputations ("thinning").

**Step 3: Imputing missing data**

For a subject who withdrew from the study early, let $Y_1$ denote the number of events prior to withdrawal (over time $t_1$), and let $Y_2$ denote the number of unobserved events after withdrawal until the end of the study's planned treatment period (over time $t_2$). For a subject who completes the planned treatment period, $Y_1$ denotes the number of events prior to completion (over time $t_1$). Using the formula in Keene et al. 2014, the unobserved events $Y_2$ will be imputed from a negative binomial distribution with parameters $k^*$ and $p^*$, where:

- $k^* = k + Y_1$
- $p^* = \frac{(k+\varphi_1)}{(k+\varphi_1+\varphi_2)}$
- $\varphi_1$ is the expected number of events prior to withdrawal
- $\varphi_2$ is the expected number of events after withdrawal

Thus, $Y_1 + Y_2$ gives the number of exacerbations (observed and imputed) over the planned treatment period, $(t_1 + t_2)$. A random seed of 801919 will be used for the imputation.

The parameters $\varphi_1$ and $\varphi_2$ will be derived for each set of $k$ and $\beta$ sampled in ***Step 2*** under 2 different missing data scenarios, MAR and DRMI.

**Step 4: Multiple imputation algorithm**

For each scenario detailed in Step 3, the algorithm for implementing multiple imputation is:

i. Select the first set of parameters $(\hat{\beta}, \hat{k})$ from Step 2

ii. Impute $Y_2$ for each subject who discontinued from the study early, using the method outlined in Step 3

iii. Calculate $Y_3 = Y_1 + Y_2$ for all subjects, where $Y_2 = 0$ for subjects who completed the study and $Y_2 \geq 0$ for subjects who discontinued from the study early.

iv. A negative binomial regression model will be fitted using $Y_3$ as the response variable with treatment group, region, and the number of exacerbations in the previous year included as covariates. For subjects completing the planned treatment period, the offset will be the logarithm of the time at risk (in years) for exacerbation. For subjects with an imputed number of exacerbations after withdrawal, the offset will be the logarithm of the study's planned treatment period excluding the time during an observed exacerbation and the 7 days following an observed exacerbation, and 7 days for each imputed exacerbation.

v. Using the model from (iv) calculate treatment differences for the comparisons of interest

vi. Select the next set of parameters $(\hat{\beta}, \hat{k})$ from Step 2 and repeat (ii) through to (v) a further 99 times.

vii. Using Rubin's formulae (Rubin 1987; Barnard and Rubin. ), summarise the sets of treatment differences in (v) to give an overall treatment difference for the comparisons of interest with 95% confidence limits. The number of events and total time at-risk will be derived by taking the arithmetic mean of these values across the sets of data.

viii. Back-transform the estimates and 95% confidence limits to give a rate ratio and corresponding limits.

#### 8.1.1.1.4 Sensitivity analyses under alternative estimand

In addition to primary and sensitivity analyses described previously, an alternative estimand will be estimated using only the on initial randomised treatment data:

- Assumed loss of effect post discontinuation of benralizumab: This will be estimated using the DRMI controlled imputation approaches including only data from patients whilst on treatment.

Therefore, the primary analyses and sensitivity analyses will be repeated including only data from patients whilst being on initial randomised treatment, ie, excluding data once patients discontinue from randomised treatment.

For the negative binomial model fit on data after imputation, the logarithm of the maximum follow-up time subtracting the time period when patient is experiencing observed exacerbation and 7 days following an observed exacerbation serves as an offset variable. However, the time period is not imputed for imputed exacerbation events. The maximum follow-up time for patients who early withdraw from IP treatment will be hypothetical Week 56 (392 days).

A summary of reasons for patients withdrawing from the benralizumab treatment and the corresponding treatment arm used to calculate the imputation exacerbation rate under MAR and DRMI are given in Table 7. As for patients who withdraw from the study treatment, a review of each patient who discontinued randomised treatment will be carried out prior to unblinding the study where the default assumptions for DRMI as described in Table 7 may be changed. Again, a list of these patients and the assumptions made under DRMI will be documented prior to unblinding of the study.

**Table 7 Treatment arm used to perform imputations by reason for study treatment discontinuation**

| Reason for discontinuation of randomized treatment | MAR | DRMI |
|---|---|---|
| Subject decision | Benralizumab | Based on review prior to study unblinding |
| Adverse Event | Benralizumab | Placebo |
| Severe non-compliance to protocol | Benralizumab | Placebo |
| Condition under investigation worsened | Benralizumab | Placebo |
| Development of study specific discontinuation criteria* | Benralizumab | Placebo |
| Subject lost to follow-up | Benralizumab | Benralizumab |
| Other | Benralizumab | Based on review prior to study unblinding |

Note: All patients on exacerbation rate in the placebo arm are imputed using the placebo arm rate.

*Development of study-specific discontinuation criteria are based on the following: anaphylactic reaction to the IP requiring administration of epinephrine, helminth parasitic infestations requiring hospitalization, intensive care unit admission with prolonged intubation and mechanical ventilation for a COPD-related event.

Using on treatment data is easier to interpret as it is not impacted by any subsequent pattern of alternative treatments once patients discontinue from randomised treatment. Sensitivity analyses under DRMI allow for alternative assumptions to be made based on reasons for discontinuation.

#### 8.1.1.1.5 Overall summary of analyses to account for missing data

A summary of the different analyses to be carried out under different estimand and assumptions are described in Table 8.

**Table 8 Summary of analysis**

| | Treatment Policy and alternative estimands | | |
|---|---|---|---|
| **Assumption (Missingness mechanism)** | | **MAR** | **MNAR** |
| | **DL** | **MAR** | **DRMI** |
| Exacerbation rate for imputation in Benra arm[b] | No explicit imputation[a] | Benra for all reasons for withdrawal assumed to be on Benra | Placebo rate for treatment related withdrawal, otherwise Benra or based on review prior to study unblinding |
| Default definition for $\boldsymbol{p_{j,1}}$ and $\boldsymbol{p_{j,2}}$ based on $p_j = \frac{p_{j,2} - p_{j,1}p_{j,2}}{1 - p_{j,1}p_{j,2}}$ [c]. j denotes the treatment arm and i denotes the subject identifier. | | $p_{j,2} = p_{j,1}$ For all treatment arms j=B and P | $p_{\mathrm{B},2} = p_{\mathrm{P},1}$ $p_{\mathrm{P},2} = p_{\mathrm{P},1}$ for reasons above otherwise $p_{\mathrm{B},2} = p_{\mathrm{B},1}$ |

[a] Implicitly assumes unobserved rate the same as observed

[b] All patients on exacerbation rate in the placebo arm are imputed using the placebo arm rate (ie, $p_{P,2} = p_{P,1}$)

[c] Note: can be overwritten by review prior to study unblinding.

B Benralizumab 100mg; P Placebo.

Forest plots will be used to show the primary analysis results along with the missing data sensitivity and alternative estimand analysis results.

It is noted that if the primary analysis is statistically significant, it is not necessarily expected that all sensitivity analyses will also give statistically significant results. If the results of the sensitivity analyses provide reasonably similar estimates of the treatment effect to the primary analysis, this will be interpreted as providing assurance that neither the lost information nor the mechanisms which cause the data to be missing have an important effect on primary analysis conclusions. Based on these outputs and the drug's mechanism of action, the plausibility of the assumptions we make about missing data in the different analyses will be considered and described in the clinical study report.

#### 8.1.1.2 Accounting for missing data for continuous endpoints (pre-bronchodilator $FEV_1$ and SGRQ total score)

##### 8.1.1.2.1 Primary analysis under the Treatment Policy Estimand using the MAR assumption

As for the primary variable, the primary analysis of the pre-bronchodilator $FEV_1$ and SGRQ total score key secondary endpoints includes all data captured during the trial up to Week 56. The mixed-effect model for repeated measures analysis (MMRM) used is a DL approach which is valid under the MAR assumption.

#### 8.1.1.2.2 Sensitivity analysis under the Treatment Policy Estimand using MNAR assumptions

Sensitivity analyses of the MMRM will be performed for the pre-bronchodilator $FEV_1$ and SGRQ total score using controlled sequential multiple imputation methods based on pattern mixture models, as described in (Guideline on Missing Data 2010).

The method is analogous to the multiple imputation of exacerbation events and the imputation process consists of a sequence of MI steps, where each step is intended to impute missing values at 1 time-point only. This model will assume that some pre-specified subset of subjects who withdraw from the study have correlations with future (unobserved) visits similar to subjects in the placebo arm. As for the exacerbation events, this allows us to assess various deviations from the MAR assumption.

The assumptions that will be used to impute the missing data who withdraw early are as follows:

(c) **MAR:** Assumes that the trajectory for patients who dropped out in each arm is similar to those observed in their own treatment arm

(d) **DRMI:** Assumes that the trajectory for patients in the benralizumab arm who dropped out for a treatment related reasons (according to the same classification as for the DRMI analysis of the primary endpoint) is similar to that of the placebo subjects, whereas the remaining patients who has dropped out are imputed assuming MAR.

Approach b) can be considered more conservative than the approach for the primary analysis because the assumptions mean that as soon as subjects withdraw for a treatment related reason, they begin to worsen immediately.

The MNAR imputation is achieved by only using appropriate data at each stage of the imputation. Imputation will be done in 2 steps, the non-monotone (intermediate) missing SGRQ total score and $FEV_1$ values will be imputed first [Markov chain Monte Carlo (MCMC) method is used to partially impute the data using SAS PROC MI] and then the missing value at each visit will be imputed using a sequential regression method (using *MONOTONE REG* option of *SAS PROC MI*).

For example, to impute missing values at time t for subjects in the benralizumab arm, that dropped out due to an AE, include only placebo observations up to and including time t, plus observations from subjects in the benralizumab arms, that dropped out due to an AE, up to and including time t-1. This is done for each visit, one at a time using observed data, and missing just imputed. Placebo missing observations and benralizumab observations that are not missing due to AEs are imputed assuming missing at random (MAR) and follow the pattern of observed placebo observations in each treatment arm respectively. 100 imputations will be

carried out, and a seed of 407016 will be used for the monotone imputation step and a seed of 766275 will be used for the sequential regression imputation step. The analysis of each of the imputed datasets will be as described for the primary analysis in Section 4.3.5.1 and these will be combined using SAS procedure *PROC MIANALYZE*.

To avoid possible convergence issues when fitting MMRM models to 100 imputed datasets, the estimated unstructured covariance parameters from the first imputation where the model converges will be used as the starting values to fit the models for all imputed datasets.

#### 8.1.1.2.3 Sensitivity analysis under alternative estimands

Analogously to the approach for the primary endpoint, estimands will be estimated using on-treatment data and the methods described above.

Results for continuous endpoints will be presented as per the recurrent event sensitivity analyses.

### 8.1.2 Tipping point methods

Tipping point analysis will be performed for the primary and key secondary endpoints included in the multiple testing procedure if the primary endpoint in the primary population achieves statistical significance. If statistical significance is achieved, tipping point analyses will also be performed for the primary endpoint in the overall population and each of the key secondary endpoints that achieve nominal statistical significance of 0.05.

Tipping point analyses will be performed using similar multiple imputation methodology under the treatment policy estimand using the MAR assumption. In the tipping point analyses for the exacerbation endpoints, various degrees of improvement in the placebo group δP after withdrawal, and various degrees of worsening in the benralizumab group δT after withdrawal, will be simultaneously explored.

Because of the computational intensity of conducting tipping point analyses with MMRM, tipping point analyses for SGRQ and pre-bronchodilator $FEV_1$ will be conducted in one dimension only, assessing varying degrees of worsening in the benralizumab group of δT, but with data in the placebo arm assumed MAR (i.e., δP=0). A MAR assumption is reasonable for the placebo arm in this case as it is unlikely that placebo patients who discontinue would be expected to perform better than those not discontinuing. Tipping point analyses are intended to identify the point at which the results would tip from statistically significant to not statistically significant, based on the nominal p-value.

#### 8.1.2.1 Exacerbation endpoints

For the annualized rate of moderate or severe exacerbations up to 56 weeks and the annualized rate of severe exacerbations through EOT, placebo subjects who withdraw from the study (irrespective of reason for discontinuation) will have their imputed rates multiplied by an improvement factor δP. Benralizumab subjects who withdraw from the study (irrespective of reason for discontinuation) will have their imputed rates multiplied by a worsening factor δT.

Tipping points are defined as the range of smallest values (δP, δT) which would result in a change of conclusion, the latter being assessed according to the nominal statistical significance level of 0.05 (i.e. the significance level used for the primary endpoint comparison in the multiple testing procedure).

Imputation will be performed within each treatment arm as follows, where (δP, δT) = (1, 1) corresponds to the MAR analysis:

- log(δP) will be varied from -1.5 to 0 in increments of 0.5.
- log(δT) will be varied from 0 to 1.5 in increments of 0.5.

This corresponds to values of δP between 0.22 and 1, and values of δT between 1 and 4.5. Based on the unblinded data following the clinical data lock, the range of (δP, δT) may be updated.

If statistical significance is maintained among the matrix of possible δ combinations, no tipping point will be identified. If a tipping point is observed with analysis at 0.5 increments, the δ values will be further refined down to 0.25 increments for the relevant interval. For example, if a tipping point is identified when increasing log(δA) from 1 to 1.5, the matrix will be expanded to also include the value log(δA) = 1.25.

#### 8.1.2.2 Continuous endpoints (pre-bronchodilator $FEV_1$ and SGRQ total score)

For the change from baseline in SGRQ total score up to 56 weeks and the change from baseline in pre-bronchodilator $FEV_1$ up to 56 weeks, placebo subjects who withdraw from the study (irrespective of reason for discontinuing IP) will have their first imputed value improved by δP. This results in a one-time shift towards a better value in the outcomes of placebo subjects that withdraw from the study after a given visit. Benralizumab subjects who withdraw from the study (irrespective of reason for discontinuing IP) will have their first imputed value worsened by δT. This results in a one-time shift towards a worse value in the outcomes of benralizumab subjects that withdraw from the study after a given visit.

The control imputations will be done in 2 steps:

i. The non-monotone (intermediate visits) missing values will be imputed first, assuming MAR (the Markov chain Monte Carlo [MCMC] method will be used to partially impute the data using SAS PROC MI).

ii. Then, the remaining monotone missing values at each visit will be imputed using the sequential regression method (using the MONOTONE REG option in PROC MI). At each iteration, missing values will be imputed sequentially, one time-point at a time.

Step (i) will first be applied to the non-monotone missing values, exactly as specified above for control imputation.

For step (ii), the sequential monotone regression method will also be applied. To impute missing values at time t for subjects in the placebo arm, an imputation model which uses placebo subjects who had observed data at time t will be used, and the one-time improvement δP applied to this. To impute missing values at time t for subjects in the benralizumab arm, an imputation model which uses benralizumab subjects who had observed data at time t will be used, and the one-time worsening δT applied to this. In other words, imputation will be performed within each treatment arm, and therefore (δP, δT) = (0, 0) corresponds to the MAR analysis.

**For the change from baseline in pre-bronchodilator $FEV_1$:**

- δP will not be varied due to computational intensity of the analysis (δP =0, i.e. MAR)
- δT will be varied from 0 to -0.5 L in increments of 0.1 mL.

**For the change from baseline in SGRQ total score:**

- δP will not be varied due to computational intensity of the analysis (δP =0, i.e. MAR)
- δT will be varied from 0 to -12 in increments of 2.

If a tipping point is observed with the analysis increments noted above, smaller increments may be considered to determine the tipping point more precisely.

Of note, imputed values will not be impossible values (e.g. negative SGRQ score). Thus, the values will be imputed from a truncated distribution.

## 8.2 Partial dates for adverse events and prior/concomitant medications

Dates missing the day, or both the day and month of the year will adhere to the following conventions to classify treatment-emergent AEs and to classify prior/concomitant medications:

Partial/Missing Start Date

- *Missing day* – The missing start day will be set to:
  - First day of the month of occurrence if the start YYYY-MM is after the YYYY-MM of first study treatment.
  - The day of the first study treatment if the start YYYY-MM is the same as YYYY-MM of the first study treatment.
  - The date of informed consent if the onset YYYY-MM is before the YYYY-MM of the first study treatment.
- *Missing day and month* – If the start date is missing both the day and month, the start date will be set to:
  - January 1st of the year of occurrence.
  - The date of the first study treatment if the start year is the same as the year of the first study treatment.
- *Completely missing* – If the start date is completely missing, the date will be set to:
  - The date of first study treatment.
  - January 1st of the same year as the end date, if the end date suggests that the start date could be prior to the date of first study treatment.

Partial/Missing End Date

- *Missing day* – The missing end day will be set to:
  - Death date if the patient died in the same month.
  - The last day of the month of the occurrence if the end YYYY-MM is after the YYYY-MM of the first study treatment.
  - The day of last study treatment if the YYYY-MM of occurrence is the same as the last study treatment.
- *Missing day and month* – If the end date is missing both the day and month, the date will be set to:
  - Date of death if the patient died in the same year.
  - December 31st of the year of occurrence.

  - Last study treatment date if the year of occurrence is the same as the last study treatment date.

- *Completely missing* – If the end date is completely missing, the following rules will apply:
  - If the end date is completely missing and recorded as ongoing, the end date will not be imputed.
  - If the end date is completely missing and not recorded as ongoing, the date will be set to:
    - The date of the first study treatment if the start date is prior to the date of first study treatment.
    - The date of last visit, if the start date is on or after the date of first study treatment.

## 8.3 Analysis plan for ADA data

ADA samples will be collected at scheduled visits shown in the CSP and ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titre). The ADA result from each sample will be reported as either positive or negative. If the sample is positive, the ADA titre will be reported as well. In addition, the presence of neutralizing antibody (nAb) will be tested in all ADA-positive samples using a ligand binding assay. The nAb results will be reported as positive or negative.

Since the ADA samples from patients in China sites are tested in different assay from the rest of world, the ADA summary tables will exclude patients from China sites. The positive ADA data from patients in China site will only be included in key subject information table.

Subjects with a missing baseline ADA assessment will be assumed to be ADA negative at baseline as a conservative approach to ensure that all subjects are included in all analyses. If a positive ADA titre result is reported as ≤50 in sites other than in mainland China, then the titre will be imputed as 50 for titre summaries. ADA results from samples collected post-dose instead of pre-dose on an IP administration day are considered unreliable and should be excluded from all derivations.

For each subject, the following ADA responses will be evaluated through EOT:

- Subjects who are ADA positive at any time during the study, including baseline and/or post-baseline (also generally referred to as **ADA positive**). The proportion of ADA-positive subjects in a population is known as **ADA prevalence**.
- Subjects who are ADA negative at all assessments, including baseline and post-baseline (also generally referred to as **ADA negative**).
- Subjects who are ADA positive at baseline only.
- Subjects who are ADA positive at baseline and at least one post-baseline assessment.
- Treatment-emergent ADA positive (TE-ADA+) (referred to as **ADA incidence**). A positive post-baseline result and either of the following statements holds:
  - Baseline is ADA negative and at least one post-baseline assessment is ADA positive. This is called **treatment-induced ADA positive**.

  - Baseline is ADA positive, and the baseline titre is boosted by greater than the variability of the assay (i.e. ≥ 4-fold increase) at ≥1 post-baseline timepoint. This is called **treatment-boosted ADA positive**.

- Subjects who are ADA positive but not following the conditions above for treatment emergent ADA positive (also referred to as **non-TE ADA positive**).

- Subjects who are **persistently ADA positive**, which is defined as ADA negative at baseline and having at least 2 post-baseline ADA positive measurements with ≥ 16 weeks between first and last positive, or an ADA positive result at the last available post baseline assessment.

- Subjects who are **transiently ADA positive**, defined as ADA negative at baseline and at least one post- baseline ADA positive measurement and not fulfilling the conditions for persistently positive.

- nAb prevalence; defined as nAb positive at any visit including baseline and/or post-baseline (also referred to as nAb positive)

- nAb incidence; defined as nAb negative at baseline (or ADA negative at baseline) and nAb positive at any post-baseline visit. Patients who are ADA-negative at baseline are included to ensure that all patients who are nAb positive for the first-time post-baseline satisfy this definition, given that all patients who are ADA negative at baseline will not have a nAb result reported.

- Subjects who are treatment-emergent ADA positive with maximum post-baseline titre > median of maximum post-baseline titres. The median of maximum post-baseline titres will be calculated based on the maximum post-baseline titre of each ADA positive subject.

The responses above will be summarized as counts and percentages by treatment group, including placebo. The maximum ADA titre over the study period will also be summarized for patients in each of the ADA positive response categories listed above. The maximum titre will be derived based on all available ADA titres reported for each subject, including any unscheduled assessments.

ADA positive response and titre will be summarized at baseline and at all scheduled post-baseline visits by treatment group using derived visit windows (refer to Section 3.1.1 for detailed definition of visit windows). In the event a patient has more than one result within a given visit window, the maximum ADA titre will be used in the by-visit summary. In

addition, the ADA response will be presented cumulatively. The cumulative ADA response is positive for a specific visit if a positive ADA result is detected at any time point up to and including the specific visit. If all ADA results are negative up to the specific visit, then the cumulative ADA response is negative for that visit. A summary of the number and percentage of patients who are ADA positive at a post-baseline assessment for the first time by visit will also be presented. A line plot of the proportion of subjects who are ADA positive at each visit will be provided.

The proportion of patients with positive nAb response will be summarised by visit.

Key patient information will be listed for patients with positive ADA results, including overall ADA category during the study, nAb status, ADA result, titer, benralizumab serum concentration, and eosinophil level.

All analyses will be conducted on the safety analysis set by treatment group unless otherwise specified.

**ADA and eosinophil levels**

Eosinophil levels will be summarised by visit for the following ADA response categories of patients: treatment-emergent ADA positive, ADA negative, ADA persistently positive, non-TE ADA positive, ADA transiently positive, TE-ADA positive with maximum post-baseline titre > median of maximum post-baseline titre, nAb-positive.

A line plot of eosinophil levels by visit and ADA status will also be presented.

**ADA and efficacy**

The effects of ADA on the primary endpoint in PFAS and OFAS will be evaluated through summary statistics by ADA status (treatment-emergent ADA positive, ADA negative, ADA persistently positive ADA transiently positive, TE-ADA positive with maximum post-baseline titre > median of maximum post-baseline titre, nAb-positive).

**ADA and safety**

Adverse events overall summary and hypersensitivity during the study will be summarised by ADA status (ADA negative, treatment-emergent ADA positive, non-TE ADA positive).

**ADA and PK**

Benralizumab serum concentrations will be summarised by visit and ADA status (treatment-emergent ADA positive, ADA negative, ADA persistently positive, ADA transiently positive, TE-ADA positive with maximum post-baseline titre > median of maximum post-baseline titre, nAb-positive) for patients in the PK analysis set.

## 8.4 Efficacy estimands

**Table 9 Overview of objectives and estimand attributes**

| Statistical category | Endpoint | Population | Intercurrent event strategy | Population level summary (analysis) | Details in section |
|---|---|---|---|---|---|
| **Objective 1:** To evaluate the effect of benralizumab 100 mg on COPD exacerbations in patients with moderate to very severe COPD | | | | | |
| Primary analysis– primary estimand | Annualized rate of moderate/severe COPD exacerbations up to Week 56 | • PFAS<br>• OFAS | Treatment policy (i.e., included regardless of whether subjects remain on randomised treatment) | Rate ratio for interventions (NB model) | 4.3.5.1 |
| Sensitivity - primary estimand | Annualized rate of moderate/severe COPD exacerbations up to Week 56 | • PFAS<br>• OFAS | Withdrawal from study (as per primary estimand) assumed to be MAR | Rate ratio for interventions (NB model with MI from same randomised arm off-treatment) | 8.1.1.1 |
| Sensitivity - primary estimand | Annualized rate of moderate/severe COPD exacerbations up to Week 56 | • PFAS<br>• OFAS | Withdrawal from study (as per primary estimand) assumed to be MNAR | Rate ratio for interventions (NB model with drop-out reason-based MI) | 8.1.1.1 |
| Sensitivity - primary estimand<br>Tipping point | Annualized rate of moderate/severe COPD exacerbations up to Week 56 | • PFAS<br>• OFAS | Treatment policy (i.e., included regardless of whether subjects remain on randomised treatment) | Rate ratio for interventions (NB model) | 8.1.2.1 |
| Sensitivity - alternative estimand | Annualized rate of moderate/severe COPD exacerbations excluding treated with antibiotics alone up to Week 56 | • PFAS<br>• OFAS | Remained adherent to intervention (on-treatment) | Rate ratio for interventions (NB model) | 8.1.1.1 |

| Statistical category | Endpoint | Population | Intercurrent event strategy | Population level summary (analysis) | Details in section |
|---|---|---|---|---|---|
| Supportive analysis–primary estimand | Annualized rate of moderate/severe COPD exacerbations through EOT | • PFAS<br>• OFAS | Treatment policy (i.e., included regardless of whether subjects remain on randomised treatment) | Rate ratio for interventions (NB model) | 4.3.5.3 |
| **Objective 2: To evaluate the effect of benralizumab 100 mg on severe COPD exacerbations (leading to hospitalization or death)** | | | | | |
| Primary analysis - primary estimand | Annualized rate of severe COPD exacerbations through EOT | • PFAS<br>• OFAS | Treatment policy (i.e., included regardless of whether subjects remain on randomised treatment) | Rate ratio for interventions (NB model) | 4.3.6.1 |
| Sensitivity - primary estimand | Annualized rate of severe COPD exacerbations through EOT | • PFAS<br>• OFAS | Withdrawal from study (as per primary estimand) assumed to be MAR | Rate ratio for interventions (NB model with MI from same randomised arm off-treatment) | 8.1.1.1 |
| Sensitivity - primary estimand | Annualized rate of severe COPD exacerbations through EOT | • PFAS<br>• OFAS | Withdrawal from study (as per primary estimand) assumed to be MNAR | Rate ratio for interventions (NB model with drop-out reason-based MI) | 8.1.1.1 |
| Sensitivity - primary estimand<br>Tipping point | Annualized rate of severe COPD exacerbations through EOT | • PFAS<br>• OFAS | Treatment policy (i.e., included regardless of whether subjects remain on randomised treatment) | Rate ratio for interventions (NB model) | 8.1.2.1 |
| Alternative estimand | Annualized rate of severe COPD exacerbations up to IP discontinuation or EOT | • PFAS<br>• OFAS | Remained adherent to intervention (on-treatment) | Rate ratio for interventions (NB model) | 8.1.1.1 |

| Statistical category | Endpoint | Population | Intercurrent event strategy | Population level summary (analysis) | Details in section |
|---|---|---|---|---|---|
| Supportive – primary estimand | Annualized rate of severe COPD exacerbations up to Week 56 | • PFAS<br>• OFAS | Treatment policy (i.e., included regardless of whether subjects remain on randomised treatment) | Rate ratio for interventions (NB model) | 4.3.6.1 |
| **Objective 3: To evaluate the effect of benralizumab 100 mg on health status/health-related quality of life** | | | | | |
| Primary analysis - primary estimand | SGRQ total score change from baseline at Week 56 | • PFAS<br>• OFAS | Treatment policy (i.e., included regardless of whether subjects remain on randomised treatment) | Mean difference between interventions (LSMD in CFB MMRM (by visit)) | 4.3.6.2 |
| Sensitivity - primary estimand | SGRQ total score change from baseline at Week 56 | • PFAS<br>• OFAS | Withdrawal from study (as per primary estimand) assumed to be MAR | Mean difference between interventions (LSMD from CFB MMRM with MI from same randomised arm off-treatment) | 8.1.1.2 |
| Sensitivity - primary estimand | SGRQ total score change from baseline at Week 56 | • PFAS<br>• OFAS | Withdrawal from study (as per primary estimand) assumed to be MNAR | Mean difference between interventions (LSMD from CFB MMRM with drop-out reason-based MI) | 8.1.1.2 |
| Sensitivity - primary estimand<br>Tipping point | SGRQ total score change from baseline at Week 56 | • PFAS<br>• OFAS | Treatment policy (i.e., included regardless of whether subjects remain on randomised treatment) | Mean difference between interventions (LSMD from CFB MMRM at Week 56) | 8.1.2.2 |

| Statistical category | Endpoint | Population | Intercurrent event strategy | Population level summary (analysis) | Details in section |
|---|---|---|---|---|---|
| Alternative estimand | SGRQ total score change from baseline at Week 56 | • PFAS<br>• OFAS | Remained adherent to intervention (on-treatment) | Mean difference between interventions (LSMD from CFB MMRM at Week 56) | 8.1.1.2 |
| Supportive analysis–primary estimand | SGRQ total score change from baseline through EOT | • PFAS<br>• OFAS | Treatment policy (i.e., included regardless of whether subjects remain on randomised treatment) | Mean difference between interventions (LSMD in CFB MMRM (by visit)) | 4.3.6.2 |
| **Objective 4: To evaluate the effect of benralizumab 100 mg on pulmonary function** | | | | | |
| Primary analysis - primary estimand | Pre-bronchodilator $FEV_1$ change from baseline at Week 56 | • PFAS<br>• OFAS | Treatment policy (i.e., included regardless of whether subjects remain on randomised treatment) | Mean difference between interventions (LSMD in CFB MMRM (by visit)) | 4.3.6.3 |
| Sensitivity - primary estimand | Pre-bronchodilator $FEV_1$ change from baseline at Week 56 | • PFAS<br>• OFAS | Withdrawal from study (as per primary estimand) assumed to be MAR | Mean difference between interventions (LSMD from CFB MMRM with MI from same randomised arm off-treatment) | 8.1.1.2 |
| Sensitivity - primary estimand | Pre-bronchodilator $FEV_1$ change from baseline at Week 56 | • PFAS<br>• OFAS | Withdrawal from study (as per primary estimand) assumed to be MNAR | Mean difference between interventions (LSMD from CFB MMRM with drop-out reason-based MI) | 8.1.1.2 |

| Statistical category | Endpoint | Population | Intercurrent event strategy | Population level summary (analysis) | Details in section |
|---|---|---|---|---|---|
| Sensitivity - primary estimand<br>Tipping point | Pre-bronchodilator $FEV_1$ change from baseline at Week 56 | • PFAS<br>• OFAS | Treatment policy (i.e., included regardless of whether subjects remain on randomised treatment) | Mean difference between interventions (LSMD from CFB MMRM at Week 56) | 8.1.2.2 |
| Alternative estimand | Pre-bronchodilator $FEV_1$ change from baseline at Week 56 | • PFAS<br>• OFAS | Remained adherent to intervention (on-treatment) | Mean difference between interventions (LSMD from CFB MMRM at Week 56) | 8.1.1.24.3.6.3 |
| Supportive analysis–primary estimand | Pre-bronchodilator $FEV_1$ change from baseline through EOT | • PFAS<br>• OFAS | Treatment policy (i.e., included regardless of whether subjects remain on randomised treatment) | Mean difference between interventions (LSMD in CFB MMRM (by visit)) | 4.3.6.3 |

CFB Change from Baseline; $FEV_1$ Forced expiratory volume in 1 second; EOT = End of treatment; NB = Negative binomial; LSMD = Least Squares Mean Difference; MMRM = Mixed model for repeated measures; PFAS = Primary Full Analysis Set (patients with ≥3 prior exacerbations); OFAS = Overall Full Analysis Set (patients with ≥2 prior exacerbations)

## 8.5 Inhaled Corticosteroids Dose Conversion

Total daily dose of ICS at randomization will be classified as high dose or lower dose according to equivalent Fluticasone propionate dose. If a patient takes more than one medication containing ICS, the doses will be standardized according to equivalent dose specified in table below. After conversion, the total daily dose for inhaled corticosteroid will be calculated and classified as high dose (≥ 500 mcg/day) or lower dose (< 500 mcg/day).

**Table 10 Inhaled Corticosteroids Dose Conversion**

| ICS component | Conversion factor |
|---|---|
| Fluticasone propionate | 1 |
| Fluticasone propionate HFA (Flovent HFA) | 1.4 |
| Fluticasone furoate | 2.5 |
| Budesonide | 0.63/ 0.78 |
| Budesonide (nebulized) | 0.5 |
| Beclomethasone | 0.5 |
| Beclomethasone (Trimbow) | 1.25 |
| Beclomethasone extra-fine particles and HFA (Fostair, QVAR) | 1.04/ 1.25 |
| Ciclesonide | 1.56 |
| Mometasone | 1.14 |
| Flunisolide | 0.25 |
| Triamcinolone | 0.25 |

## 8.6 Systemic Corticosteroids Dose Conversion

All systemic corticosteroids and depot injection of corticosteroid collected in COPDEX eCRF administered to treat COPD exacerbation during the study will be converted to a prednisone equivalent dose. Systemic corticosteroids are defined as medications with coding ATCDTXT in ("GLUCOCORTICOIDS", "CORTICOSTEROIDS FOR SYSTEMIC USE, COMBINATIONS)" and ATC code in (H02AB, H02BX) with one of the following routes of administration: PARENTERAL, INTRAVENOUS, INTRAMUSCULAR, SUBCUTANEOUS, ORAL. All systemic steroids will be converted to a prednisone equivalent dose by multiplying the total daily dose (in mg) of the respective medication with its corresponding conversion factor in Table 11. All converted systemic steroid doses given on the same day will be summed to create the total daily dose.

**Table 11 Systemic Corticosteroids Dose Conversion**

| Medication (preferred term) | Conversion factor | Numerical Conversion factor |
|---|---|---|
| Betamethasone | 10/1.2 | 8.3333 |
| Betamethasone dipropionate | 10/1.2 | 8.3333 |
| Betamethasone sodium phosphate | 10/1.2 | 8.3333 |
| Cortisone | 1/5 | 0.2 |
| Deflazacort | 1/1.2 | 0.83333 |
| Dexamethasone | 10/1.5 | 6.6667 |
| Dexamethasone sodium phosphate | 10/1.5 | 6.6667 |
| Hydrocortisone | 1/4 | 0.25 |
| Hydrocortisone sodium succinate | 1/4 | 0.25 |
| Meprednisone | 5/4 | 1.25 |
| Methylprednisolone | 5/4 | 1.25 |
| Methylprednisolone acetate | 5/4 | 1.25 |
| Methylprednisolone sodium succinate | 5/4 | 1.25 |
| Prednisolone | 1.0 | 1.0 |
| Prednisolone sodium succinate | 1.0 | 1.0 |
| Prednisone | 1.0 | 1.0 |
| Prednisone acetate | 1.0 | 1.0 |
| Triamcinolone acetonide | 5/4 | 1.25 |

Note: For the ATC category "*CORTICOSTEROIDS FOR SYSTEMIC USE, COMBINATIONS*," use the glucocorticoid conversion factor to convert the medication to a prednisone equivalent dose. For example, in "*BETAMETHASONE; LORATADINE*" the conversion factor of BETAMETHASONE (10/1.2) is used as the conversion factor for the medication.

## 8.7 CCI [redacted]

### 8.7.1 CCI [redacted]

CCI [redacted]
CCI [redacted]

**Table 12** CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

### 8.7.2 CCI

CCI

CCI

CCI

CCI

CCI

CCI

**Table 13** CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

### 8.7.3 CCI

CCI

CCI

CCI

CCI

CCI

Signature Page for VV-RIM-06779990 System v2.0
D3251C00014 Statistical Analysis Plan Edition 3

| | |
|---|---|
| Approve: Document Level Task<br>Verdict: Approved | PPD<br>Content Approval<br>13-Dec-2024 09:47:37 GMT+0000 |

| | |
|---|---|
| Approve: Document Level Task<br>Verdict: Approved | PPD<br>Content Approval<br>13-Dec-2024 12:49:20 GMT+0000 |

Signature Page for VV-RIM-06779990 System v2.0
D3251C00014 Statistical Analysis Plan Edition 3