Clinical Study Protocol	
Drug Substance	Benralizumab
Study Code	D3251C00014
Version	6.0
Date	6 February 2023

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 (RESOLUTE)

Sponsor:

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VERSION HISTORY

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	6-Feb-2023
Amendment 4	21-Jun-2022
Amendment 3	19-Jan-2021
Amendment 2	29-Jul-2020
Amendment 1	02-Dec-2019
Original Protocol	24-Apr-2019

Amendment 5 (6-Feb-2023)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2(13) as it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The CSP has been amended to comply with the European Union Clinical Trials Regulation [EU CTR]: (EU) No 536/2014 requirements.

Version 6.0, 6 February 2023			
Section # and name	Description of change	Brief rationale for change	Substantial /Non-substantial
CSP front page	EU CT Number was added on the CSP front page: 2022-503050-39-00	Conformance with EU CTR.: Regulation (EU) No 536/2014	Non-substantial
Section 1.1, Table 2: Schedule of activities after Week 56, Phone contact	Requirement to collect: Supplemental oxygen status and Smoking status during a phone Visit removed.	Correction of error: Per original study design Supplemental oxygen status and Smoking status should be collected during treatment Visits what is reflected by EDC design. The "X" mark has been inadvertently placed in table.	Non-substantial
Section 4.1.2 "Run-in Period (enrolment up to randomization)	Antibiotics included in following COPD exacerbation washout guidance: "If patient experiences a COPD exacerbation during the screening period, at least 2 weeks should elapse between the treatment end date (e.g. last dose of systemic corticosteroids treatment and/or antibiotics and/or end of hospitalization, whichever is later) and the next run-in visit prior to randomization." Systemic corticosteroids included in following pneumonia washout guidance: "In the case	Ensuring the correct understanding of COPD exacerbation and pneumonia treatment washout guideline.	Non-substantial

	of pneumonia during run-in, at least 6 weeks should elapse between the event end date (e.g. last dose of systemic corticosteroids and/or antibiotics treatment and/or end of hospitalization) and the next run-in visit prior to randomization".		
Section 4.4 "End of study Definition"	New template text added: definition of the end of the study per the European Union and the FDA.	The "End of the Study" definition as per FDA and EU guidance was added for the clinical trial transparency purposes aligning with the new AstraZeneca CSP template.	Non-substantial
Section 6.5.4, Table 6: "Allowed, restricted, and prohibited concomitant medication": Systemic corticosteroids (tablets, suspension, or injections)	Restriction shortened from 4 weeks to 2 weeks as follows: "Disallowed within 2 weeks prior to randomization and for other reasons throughout the study".	Correction of error: The washout period post a COPD exacerbation that occurs during the run-in period, treated with systemic corticosteroids and/or antibiotics in Table 6, was not aligned with the changes made to the previous protocol version 5.0 (Section 4.1.2). The error in table 6 is now corrected to reflect the 2-week washout period.	Non-substantial
Section 6.5.4, Table 6: "Allowed, restricted, and prohibited concomitant medication": Antibiotics	Removal of following wording: "In all other cases ≥6 weeks wash-out period should be in place after the last dose of antibiotic and prior to randomization." and corresponding footnote: "Topical antibiotics with minimal systemic absorption do not	Correction of error: The washout period post a COPD exacerbation that occurs during the run-in period, treated with systemic corticosteroids and/or antibiotics in Table 6, was not aligned with the changes made to the previous protocol version 5.0 (Section 4.1.2). The error in table 6 is now	Non-substantial

	require a washout period. Upon the agreement from AZ study physician the antibiotics washout period may be shorten if antibiotics taken for non-respiratory conditions such as: surgical prophylaxis, dental procedures etc.”	corrected to reflect the 2-week washout period.	
Section 8.4.4 Overdose	New template text was added.	Changes were made to comply with AstraZeneca new CSP template guidelines amended to adhere to the EU CTR: Regulation (EU) No 536/2014 requirements.	Non-substantial
Section 8.4.6: Medication Error and Appendix B8: Medication Error	New template text was added. Included guideline for Drug Abuse and Drug Misuse	Changes were made to comply with AstraZeneca new CSP template guidelines amended to adhere to the EU CTR: Regulation (EU) No 536/2014 requirements.	Non-substantial
Appendix A1: Regulatory and Ethical Considerations (Regulatory Reporting Requirements for Serious Breaches)	New template text was added.	Changes were made to comply with AstraZeneca new CSP template guidelines amended to adhere to the EU CTR: Regulation (EU) No 536/2014 requirements.	Non-substantial
Appendix A3: Informed Consent Process	Removal of following wording: “If a patient’s partner becomes pregnant during or within 12 weeks after the study, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the	Correction of error. Based on the increased knowledge on the safety profile of benralizumab, the restriction regarding potential paternal exposure to the drug has been alleviated in Product Specific Safety Requirements document. Accordingly, full section 8.4.3.2 “Paternal exposure” has been removed from the CSP v5.0 as no longer relevant. Removed wording was inadvertently present in CSP v5.0 and	Non-substantial

	pregnancy accordingly."	referred to no longer existent 8.4.3.2 "Paternal exposure" section.	
Appendix A5: Dissemination of Clinical Study Data Appendix A6: Data Quality Assurance (Document retention period aligned to GRAD)	New template text was added.	Changes were made to comply with AstraZeneca new CSP template guidelines amended to adhere to the EU CTR: Regulation (EU) No 536/2014 requirements.	Non-substantial
Throughout	Minor editorial changes	Correction of typos, omissions, and grammatical errors	Non-substantial

Version 5.0, 21 June 2022			
Section # and name	Description of change	Brief rationale for change	Substantial /Non-substantial
1.1 (Schedule of Activities)	Footnote "m" removed: "No CCI CCI samples will be collected at IPD visits and visits thereafter for patients who discontinue IP early."	Correction of error as no samples were intended to be collected in former version of the CSP.	Non-substantial
1.1 (Schedule of Activities)	Footnote "m" added: "CCI should not be collected during Visit 17."	Clarification regarding the collection of CCI samples for CCI .	Non-substantial
1.1 (Schedule of Activities)	Footnote "n": Removal of additional pre-BD PFT during run-in after FEV1 stability is established.	Reduction of patient burden without impacting eligibility criteria.	Non-Substantial
1.1 (Schedule of Activities) 8.1.3 Patient-reported Outcomes.	Reduction of SGRQ, CAT, EQ-5D-5L to every 24 weeks (instead of 8 weeks) after Week 56.	Reduction of Patients' burden without impacting the endpoint.	Non-substantial
1.1 (Schedule of Activities), 1.2 Synopsis - Table 3 Study objectives 2.3 Benefit/risk assessment Table 4 Study objectives	Addition of CCI CCI and the endpoint for patients with a successful CCI CCI from mechanistic sub-study to primary protocol.	Incorporation of the mechanistic sub-study endpoint in the protocol as an exploratory endpoint.	Substantial
1.1 (Schedule of Activities) 8.8 (Biomarkers)	Additional blood volume for exploratory analysis of CCI at BL (baseline – Visit	Incorporation of the mechanistic sub-study assessment in the protocol as part of the exploratory biomarker endpoint.	Substantial

	3) and Week 24 (Visit 9).		
1.1 (Schedule of Activities)	Footnote “r” added	Clarification regarding IP administration during week 56 of the last patient	Non-substantial
1.1 (Schedule of Activities) 1.2 Synopsis; Table 3 Study Objectives 1.2 Synopsis; Overall Design 2.3 Benefit/risk assessment 4.1 Overall Design 4.1.2 Run-in Period (enrolment up to randomization); Visit 1 4.1.2 Run-in Period (enrolment up to randomization); Visit 2 5.1 Inclusion Criteria 8 Study Assessments and Procedures 8.8 Biomarkers 8.9.1 Biomarker assessments for Mechanistic Sub-study only 8.11.2 Chest CT scan/X-ray 8.11.4 Lung function assessments for Mechanistic Sub-Study only 8.4.3.2 Paternal exposure 9.2.2 Sample size determination for the sub-study	Removal of mechanistic Sub-study wording/section.	The mechanistic sub-study is cancelled due to recruitment challenges related to the COVID19 pandemic. No patients were randomized to the mechanistic sub-study; therefore, there is no impact on patients participating in the trial.	Substantial
1.2 Synopsis	Change of estimated date of last patient completion from Q1 2024 to Q2 2025	Prolongation of recruitment due to recruitment challenges related to the COVID19 pandemic.	Non-substantial

4.1.2 Run-in Period (enrolment up to randomization)	Reduction of the washout period from 6 to 2 weeks after COPD exacerbation.	The literature shows that most COPD exacerbations recover in 2 weeks. The shorter washout reduces the risk of new exacerbations during the run-in.	Non-substantial
4.1.2 Run-in Period (enrolment up to randomization) 5.1 Inclusion criteria	Defining 2 weeks as a minimum time required to confirm the patient's compliance with background medication therapy.	Defining time required to confirm patient's compliance with background medication therapy in case of issues with a handheld device preventing the correct documentation during the run-in period.	Non-substantial
5.2 Exclusion criteria (#22); Footnote: "1". 6.5.4 Restrictions (Table 6: Allowed, restricted, and prohibited concomitant medication)	Allow the use of certain marketed biological products during the study.	To enable patients with specific co-morbidities to participate in the study.	Non-substantial
5.4 Screen Failures Appendix I – I2	Individuals who screen fail due to inclusion criteria (4-15) might be re-screened once without additional approval from the AZ study unless there was a significant protocol issue during the run-in/screening period during the first enrolment.	To clarify the process of patients' rescreening.	Non-substantial
6.1 Treatments administered	IP injection rotation documentation requirement alleviated.	IP administration aligned with the product label and current knowledge.	Non-substantial
6.1.1 IP administration re-scheduling	Allow IP administration during COPD exacerbation, infection, or fever unless contra-indicated.	IP administration aligned with the product label and current knowledge.	Non-substantial

8.4.3 Pregnancy 8.4.3.1 Maternal exposure Appendix B	Congenital abnormalities changed to congenital anomalies.	To align with AZ standards.	Non-substantial
8.4.3.2 Paternal exposure	Section removed	Based on increased safety knowledge, it's no longer relevant.	Non-substantial
8.4.5 Medical Device Deficiencies Appendix J	Updating Device Deficiency Reporting	Comply with device deficiency regulatory reporting	Non-substantial
8.11.2 Chest CT scan/X-ray	Removal of CCI CCI CCI CCI CCI CCI CCI CCI	CCI CCI CCI CCI CCI	Non-substantial
9.2 Sample Size determination	Removal of power requirements (i.e., at least 80% of power) for severe exacerbation that led to a reduction of sample size for the patient population. Update to describe the powers that can be achieved with the reduced sample size under a range of severe exacerbation rate assumptions for the placebo group.	In response to a substantial reduction in power for severe exacerbation caused by low severe exacerbation rates expected due to the COVID-19 pandemic.	Substantial
9.2.1 Blinded sample size reassessment	Update to potentially have a single BSSR on severe exacerbations before the last patient completes the Week 56 visit. As a result of the reassessment, the	Revision aligns with the decision to reduce the overall sample size while still having the potential to be sufficiently powered for the secondary endpoint of severe exacerbations.	Substantial

	last patient last visit may be extended to accrue additional severe exacerbation events. But it will not lead to any sample size alteration or impact on the primary endpoint.		
9.3 Population for analyses	Removal of sub-study analysis set.	The mechanistic sub-study is cancelled due to recruitment issues during the COVID19 pandemic.	Substantial
9.4.4 Methods for multiplicity control	Changes in the multiplicity control strategy.	Maximize the alpha for severe exacerbation analyses in the overall population due to the impact of COVID19 reducing expected power for this key secondary endpoint.	Substantial
Throughout	Minor editorial changes.	Correction of typos, omissions, and grammatical errors.	Non-substantial

Version 4.0, 19 Jan 2021			
Section # and name	**Description of change**	**Brief rationale for change**	**Substantial/Non-substantial**
1.1 (Schedule of Activities)	Footnote "d" of Table 1 was updated to "Informed consent for the optional Mechanistic Sub-study should be obtained prior to or on the day of V2 at the latest."	To clarify that the consent to the Mechanistic Sub-study can occur prior to V2.	Non-substantial
1.2 (Synopsis)	The language of "If a patient misses more than 2 consecutive IP doses, IP will be permanently discontinued (see Section 7.1 for details)." was removed.	Updated to align with the amendment 2 (V 3.0) change (omitted in the previous amendment).	Non-substantial
1.2 (Synopsis) and 9.2 (Sample size determination)	Baseline eosinophil count was replaced with "screening eosinophil counts".	To clarify the eosinophil counts refers to screening eosinophil values.	Non-substantial
1.2 (Synopsis) and 4.1 (Overall design)	The number of study sites and countries are updated.	To reflect the number change of countries and sites.	Non-substantial
4.1 Overall design [page #36 and 47] 4.1.2 (Run-in Period) 8.11.2 (Chest CT Scan/X-ray)	COPD exacerbation sputum samples will be collected during unscheduled visits in the clinic throughout the entire treatment period A physician qualified to read and interpret chest imaging examination results is allowed to provide clinical interpretation for the evaluation of exclusion criterion #3, in addition to the radiologist.	To reflect the COPD exacerbation sampling during the variable duration throughout the treatment period. Updated to align with the standard practice of chest imaging clinical interpretation in certain countries.	Non-substantial Non-substantial

Version 4.0, 19 Jan 2021			
Section # and name	**Description of change**	**Brief rationale for change**	**Substantial/Non-substantial**
4.1.2 (Run-in Period)	The phrase "usually with a 4-week interval" was added to the sentence "If the run-in period is extended, additional visits (Visit 2,1, 2.2, etc.) will be scheduled to re-assess eligibility and whether the patient can proceed to randomization, should continue in extended run-in, or should be excluded from the study."	To provide more specific guidance on the interval of additional run-in visits.	Non-substantial
5.1 (Inclusion Criteria)	Inclusion Criterion #6: Added requirement of at least one COPD exacerbation to occur while on triple therapy prior to enrolment. The footnote "A minimum 7-day interval is required between the end of treatment (last dose of systemic corticosteroid or antibiotics or the last day of hospitalization) of one exacerbation to the treatment start of the next exacerbation." was added to Criterion #6.	To align with changes to Inclusion criterion #7. To clarify that a minimum 7-day interval is required between exacerbations.	Non-substantial

Version 4.0, 19 Jan 2021			
Section # and name	**Description of change**	**Brief rationale for change**	**Substantial/Non-substantial**
5.1 (Inclusion Criteria), 4.1.2 (Run-in Period), and 6.5.1 (Background (maintenance) medication)	Inclusion criterion #7 - Required duration of documented use of triple (ICS/LABA/LAMA) background therapy for COPD changed from ≥ 12 month to ≥3 months immediately prior to enrollment; double ICS based therapy required for the rest of the previous year; introduced requirement at least one exacerbation in the previous year to occur while on triple therapy. Footnote "Patient who fulfill this criterion by the time of randomization are considered eligible." was removed.	The criterion was updated based on the clinical recommendation made by the Scientific Advisory Board to better reflect the targeted population.	Substantial
5.1 (Inclusion Criteria)	"SAMA taken at regularly scheduled intervals (every 6-8 hours or at least 3 times daily) will be considered equivalent to LABA." was added as a footnote.	To clarify that SAMA taken at regularly scheduled intervals is considered LAMA equivalent.	Non-substantial
5.2 Exclusion criteria	Exclusion criterion #20 is updated from "history of anaphylaxis to benralizumab or any other biological therapy" to "history of anaphylaxis to any biological therapy or vaccine".	Updated to align with the project specific safety requirements.	Non-substantial

Version 4.0, 19 Jan 2021			
Section # and name	**Description of change**	**Brief rationale for change**	**Substantial/Non-substantial**
6 (Study Treatments), 1.1 (Table 2 Schedule of Activities), 4.1.3 (Treatment period), and 8.2.2 (Pregnancy test)	New section (6.1.2 Optional self-administration of IP) was added to provide guidance on the optional self-administration after Week 56 (if allowed by local guidance). Footnote "g" was added to Table 2 (Section 1.1 SoA) to address that certain visits can be performed remotely in case of IP-self-administration Clarified procedure for urine pregnancy testing for WOCBP in case of IP self-administration	Guidance on activities to follow and footnotes were added to clarify procedures if the optional self-administration is implemented after Week 56.	Non-Substantial
6.1 (Treatment administered), 2.3 (Benefit/risk assessment), and 8.4.7 (Management of IP-related toxicities)	Requirement on observation time after IP administration was changed from 1-2 hours to 'in line with clinical practice'.	Text updated to indicate that the observation period after IP administration should be in line with clinical practice.	Non-substantial
6.5.4 (Restrictions)	A footnote was added to clarify that topical antibiotics with minimal systemic absorption do not require a washout period.	To clarify if a washout period is necessary for topical antibiotics.	Non-substantial
8.1.1 (Assessment of COPD exacerbation)	Death due to COPD will be reported as a severe COPD exacerbation irrespective of symptom worsening.	Added to clarify that death due to COPD with no recorded symptom worsening should be reported as an exacerbation event.	Non-substantial
8.3.2 (Time period and frequency for collection AE and SAE information)	The first parentheses, including the texts within, of the sentence "Adverse events (and Serious Adverse Events) will be collected from the randomization (Week 0) throughout the treatment period and including the follow-up period." was removed.	Updated to align with the new AstraZeneca study protocol template for clarity.	Non-substantial

Version 4.0, 19 Jan 2021			
Section # and name	**Description of change**	**Brief rationale for change**	**Substantial/Non-substantial**
8.4.7 (Management of IP-related toxicities) and Appendix F	The phrase "must be immediately available" was replaced with "should be available" in the sentence "Appropriate drugs, such as epinephrine, H1 and H2 antihistamines, corticosteroids, etc., and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis."	To align with clinical practice.	Non-substantial
8.4.7 (Management of IP-related toxicities)	Serum tryptase may be tested at the central laboratory, in addition to a local laboratory.	To clarify serum tryptase test may be performed at a local or central laboratory.	Non-substantial
8.8.1 (Biomarker assessment for Mechanistic Sub-study only)	The word "will" was replaced with "may" in the sentence "Results from exploratory biomarker analyses of the Mechanistic Sub-study assessments, if performed, will be reported separately from the CSR."	To align with the current Mechanistic Sub-study plan. .	Non-substantial
8.8.1 (Biomarker assessment for Mechanistic Sub-study only)	CCI [redacted] was replaced with CCI [redacted] throughout the section.	To align with the current Mechanistic Sub-study plan.	Non-substantial
8.11.2 (Chest CT scan/X-ray)	The phrase "to meet eligibility criteria" was removed from the sentence "For patients who have consented for the Mechanistic Sub-study, it is highly recommended that these patients have a new standardized CT scan (in place of a chest X-ray or historical scan) to meet eligibility criteria."	To align with the current Mechanistic Sub-study plan.	Non-substantial

Version 4.0, 19 Jan 2021			
Section # and name	**Description of change**	**Brief rationale for change**	**Substantial/Non-substantial**
9.4.1.3 (Analysis methods for secondary efficacy variable)	Repeated measurement analysis was replaced by "mixed-effect module for repeated measures analysis (MMRM)" throughout the section.	A more specific description of the statistical analysis.	Non-substantial
Throughout	Minor editorial changes	Correction of typos, omissions, and grammatical errors	Non-substantial

Version 3.0, 29 July 2020		
Section # and name	**Description of change**	**Brief rationale for change**
4.1.1 (Study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis)	New wording was added which would give guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity.	The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster, or public health crisis. This section details the measures that may be implemented if a patient is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the patient, maintaining compliance with GCP, and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption.

Version 3.0, 29 July 2020		
Section # and name	**Description of change**	**Brief rationale for change**
Appendix I	New wording is added, which would give guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity.	The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. This section details the measures that may be implemented if a patient is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the patient maintaining compliance with GCP and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption.
Throughout	Minor editorial changes	Correction of grammatical errors
1.1 (Schedule of Activities)	Footnote c updated	To allow possibility of consenting a patient electronically
1.1 (Schedule of Activities)	Footnote m was added to clarify that no serum biomarker samples will be collected at IPD visits and visits thereafter.	Updated to clarify serum biomarker sample collection in patients who discontinue IP early.
1.2 (Synopsis)	Update to International coordinating investigator business address	Updated trial center address
1.2 (Synopsis) and 2.3 (Benefit/risk assessment	Updates to Exploratory Objectives Updates to the number of countries participating in the study and to the date of last patient completed	Clarification to exploratory objectives Number of countries participating in the study increased to 26. New date of last patient completed is estimated for Q1 2024.
2.3 (Benefit/risk assessment)	Minor editorial changes were made to remove redundant wording in the potential risks section.	Redundancy removed

Version 3.0, 29 July 2020		
Section # and name	**Description of change**	**Brief rationale for change**
4.1.2 (Run-in period)	The word "inspiratory" was removed from the sentence "Patients who cannot provide a CT dated within 6 months prior to enrollment, will be scheduled for a baseline inspiratory CT at Visit 2/2.X or as soon as key eligibility criteria have been confirmed." in the subsection of chest computed tomography (CT) or chest X-ray.	Correction of an inconsistency in the protocol. Details about breath-holding maneuvers (inspiratory and expiratory) are provided in the imaging charter and radiology manual.
5.1 (Inclusion criteria)	Inclusion criterion #1: word 'written' removed	To allow for an electronic informed consent
5.1 (Inclusion criteria)	Inclusion criterion #11 was modified to include the definition of highly effective forms of birth control as of those with less than a 1% failure rate. Reference to luteinizing hormone was included in error and removed.	To follow current sponsor safety recommendations in studies with benralizumab.
5.1 (Inclusion criteria)	Inclusion criterion #15 was amended to clarify that randomization must not occur without agreement with AZ study physician/delegate, in cases of significant CAT score variations (>3) during the run-in period.	To align with section 4.1.2 and clarify that AZ study physician must be consulted in case of CAT variability.
6.1.1 (IP administration re-scheduling)	Prior to a re-scheduled IP administration, a negative urine pregnancy test result is required for WOCBP.	To clarify that, a negative urine pregnancy test is required for WOCBP prior to re-scheduled IP administration.
6.1.1 (IP administration re-scheduling) and 7.1 (Discontinuation of IP)	The criteria "Missing more than 2 consecutive IP doses (e.g., if a patient skips 2 consecutive IP doses and then misses the treatment window for the next dose, the patient will be discontinued.)" was removed	Updated to allow the patients to continue treatment if the patient misses >2 consecutive doses of IP, under exceptional circumstances.

Version 3.0, 29 July 2020		
Section # and name	**Description of change**	**Brief rationale for change**
8.1.1 (Assessment of COPD exacerbation)	Reference to major/minor symptoms and requirement for at least 2 symptoms have been removed from the symptom worsening description in COPD exacerbation definition. Sore throat, cold and fever have been removed from the list of COPD symptoms that Investigators have to capture through interviewing a patient when a COPD exacerbation is not associated with an eDiary worsening alert. Additional examples of other COPD-related symptoms (chest tightness, fatigue) have been added.	Updated to remove reference to *Anthonisen* criteria to better align with clinical practice and understanding of COPD exacerbation etiology and phenotypes, and capture exacerbations including those with atypical symptoms or only one leading symptom. Upper respiratory tract infection symptoms have been removed as not specific for COPD.
8.1.3.4 (Symptom severity questionnaire and alert system)	Investigator is responsible for contacting a patient in case of eDiary alert.	To specify Investigator's responsibilities in following up on eDiary symptom worsening alerts.
8.4.5 (Device Constituent Deficiencies)	Section name changed. Description for management of combination drug-device IMP has been added.	To ensure compliance with new regulatory guidance.
8.4.5.1 (SADE Reporting)	New section describing reporting of Serious Adverse Device Effect	To ensure compliance with new regulatory guidance.
8.5.1 (Determination of drug concentrations)	Baseline PK sample testing will not be performed on the placebo arm.	Results of placebo arm baseline PK will not provide value to the study.
8.11.4 (Lung function assessments for Mechanistic Sub-Study only)	Section included to provide high level information on the lung function assessments that are performed in the Mechanistic Sub-Study	Section added to correct omission
8.11.5 (Patient Testing Due to Public Health Crisis)	Section included if patient testing is performed due to the public health crisis, the results may be documented for this study.	Section added for test results secondary to public health crisis to be collected allowing for an evaluation of the public health crisis on the study
Appendix A (Regulatory, Ethical and Study Oversight Considerations)	New safety language 'Regulatory Reporting Requirements for SAEs'	This change reflects the latest CSP Template wording requirement

Version 3.0, 29 July 2020		
Section # and name	**Description of change**	**Brief rationale for change**
Appendix A (Regulatory, Ethical and Study Oversight Considerations)	Modified section heading. Added Suggested Text for study start date and the first act of recruitment Added Common Text regarding sponsor responsibilities on premature termination/suspension of the study.	This change reflects the latest CSP Template wording requirement
Appendix B (Adverse Event Definitions and Additional Safety Information)	New language about malignancy reporting	This change reflects the latest CSP Template wording requirement
Appendix G (Inhaled corticosteroids dose conversion)	The conversion factor of beclomethasone (Trimbow) was added.	To correct omission
Appendix G (Inhaled corticosteroids dose conversion)	Minor editorial changes	For ease of the reader

Version 2.0, 02 December 2019		
Section # and name	**Description of change**	**Brief rationale for change**
Throughout	An optional Mechanistic Sub-study planned for a subset of up to approximately 150 patients (75/treatment group) was added to the study design. High-level descriptions of the sub-study were added to various places in the protocol; key additions included all sub-study objectives and endpoints; brief overview of the study design; brief summary of the sub-study assessments; and sample size estimation. A separate sub-study manual detailed the sub-study assessments and Schedule of Activities.	To better understand the specific mechanisms underlying a treatment effect with benralizumab in patients with moderate to severe COPD, as well as a treatment effect on airway structure and function
Throughout	Correction was made to remove the word "optional" from serum biomarker assessments.	Serum biomarkers are an integral part of the study and are a mandatory assessment.
Throughout	Minor editorial and document formatting revisions; minor edits and clarifications	Minor, therefore these have not been summarized
Section 1.1 (Schedule of activities)	Activities were re-organized under major category headings in the table.	For ease of the reader
Section 1.1 (Schedule of activities)	A separate Informed Consent was added for the optional Mechanistic sub-study.	To comply with regulations
Section 1.1 (Schedule of activities)	Collection of supplemental oxygen status was added for phone FU and modified FU visits.	To correct omission
Section 1.1 (Schedule of activities) and Section 4.1.2 (Run-in period)	The duration between visits if the run-in period is extended was modified from specifying 28 (±3) days (i.e., 4 weeks) to not mandating the duration between visits except for a few specific situations.	To allow investigators flexibility to determine the optimal time between the extension visits, depending on the reason for extending the run-in period
Section 1.1 (Schedule of activities) and Section 4.1.2 (Run-in period)	Pre-bronchodilator spirometry and CAT assessments were added to Visit 2.X. Spirometry and CAT performed at Visit 3 will be used for baseline only (i.e., not for determining variability).	To assess variability of FEV_1 and CAT score during run-in
Section 1.1 (Schedule of activities), Section 8.1.3 (Patient-reported Outcomes), and Section 8.1.3.8 (Onset of Effect Questionnaire)	Correction was made to indicate that patients will complete item 1 (as opposed to item 2).	To correct error

Version 2.0, 02 December 2019		
Section # and name	**Description of change**	**Brief rationale for change**
Section 1.1 (Schedule of activities) and Section 8.2.1.1 (Other laboratory assessments)	p24 antigen was added to serology testing performed at Visit 1.	This is part of the serology panel used by the central lab
Section 1.1 (Schedule of activities) and Section 8.2.1.1 (Other laboratory assessments)	Removed analysis of serum sample for CCI [redacted] CCI [redacted]	Lack of findings in the previous Phase 3 studies suggest limited usefulness for these data
Section 1.1 (Schedule of activities) and Section 8.8 (Biomarkers)	Optional CCI [redacted] exploratory assessment was moved from the main study to the Mechanistic Sub-study.	Takes advantage of the possibility to directly correlate CCI [redacted] data with the comprehensive set of endpoints being assessed in sub-study patients.
Section 1.2 (Synopsis) - Table 3); Section 3 - Table 4 (Study objectives)	An exploratory objective for this study to evaluate the effect of benralizumab 100 mg on rescue medication use was added.	For consistency with previous Phase 3 studies in COPD patients
Section 1.2 (Synopsis) - Table 3); Section 3 - Table 4 (Study objectives)	Exploratory objectives and corresponding endpoints/variables for the Mechanistic Sub-study were added.	To expedite availability of key exploratory data for CSR and to support clinical evidence for future sBLA submission
Section 5.1 (Inclusion criteria)	Inclusion criterion #7 was amended to change the ICS component of triple background therapy from high-dose ICS (i.e. equivalent to ≥500 mcg fluticasone propionate daily as part of combination ICS/LABA/LAMA) to medium-dose ICS (i.e. equivalent to ≥250 mcg fluticasone propionate daily as part of combination ICS/LABA/LAMA)	To allow for newer fluticasone furoate formulations approved for COPD at lower (100 mcg) dosage
Section 5.1 (Inclusion criteria) and Section 5.3 (Lifestyle restrictions)	Inclusion criterion #11 was amended to stipulate that birth control method must be used from enrollment (rather than from randomization) through 12 weeks (rather than 16 weeks) after the last dose of IP.	To accommodate the usage of hormonal contraception and its required time to effectiveness; To make consistent with the time to safety follow-up.

Version 2.0, 02 December 2019		
Section # and name	**Description of change**	**Brief rationale for change**
Section 5.1 (Inclusion criteria)	Inclusion criterion #15 regarding CAT total score variability during run-in was clarified to be more specific that patients with high variability in CAT score (i.e., >3 points in either direction from previous visit) during run-in cannot be randomized and run-in period must be extended for further observation. Also, the criterion was clarified that CAT score must be >15 at Visit 1 and the last run-in visit prior to randomization for randomization to occur.	Criterion amended to be more specific.
Section 5.1 (Inclusion criteria)	Inclusion criterion #16 regarding FEV_1 stability randomization criterion removed; FEV_1 variability assessment was shifted from Visit 3 to Visit 2 during run-in to monitor FEV_1 variability during screening (compared to Visit 1) prior to randomization; variability will be monitored closely via monitoring plan.	Intent was to monitor FEV_1 variability for implausible values to better understand reasons for variability and determine actions for patients with recurrent, unexplained, implausible data. It was not to automatically exclude any/all patients with FEV_1 variability.
Section 5.2 (Exclusion criteria)	Exclusion criterion #2 was amended to clarify that asthma-COPD overlap definition is per GINA/GOLD guidelines.	To provide investigators with guidance on defining asthma-COPD overlap by referencing GINA/GOLD guidelines.
Section 5.2 (Exclusion criteria)	Exclusion criterion #9 was amended to remove exception of patients using bilevel positive airway pressure to treat sleep apnea. In clinical practice, BiPap is rarely used for sleep apnea.	To avoid incorrect enrollment of patients on BiPap for COPD or other reasons, which would be a protocol deviation
Section 5.3 (Lifestyle restrictions)	The duration that patients must abstain from donating blood, plasma, or platelets after last dose of IP was changed from 16 weeks (5 half-lives) to 12 weeks (≥5 half-lives); both durations are longer than the elimination half-life for benralizumab.	To match the duration of the safety follow-up period in this study
Section 6.5.4 (Restrictions) – Table 6	The duration that patients are prohibited from using any other marketed or investigational biologic and from receiving live attenuated vaccines was changed from 16 weeks (5 half-lives) to 12 weeks (≥5 half-lives); both durations are longer than the elimination half-life for benralizumab.	To match the duration of the safety follow-up period in this study

Version 2.0, 02 December 2019		
Section # and name	**Description of change**	**Brief rationale for change**
Section 7.1 (Discontinuation of IP)	Language requiring the investigator to consult with AZ study physician prior to IP discontinuation was modified to clarify that investigator may withhold IP if deemed urgently necessary prior to discussion with AZ and provide more detailed guidance.	To allow the investigator greater flexibility to act quickly in cases deemed urgent.
Section 8.4.2 (Regulatory Reporting Requirements for SAEs)	A summary of reporting obligations in the case of SAEs for the investigator and the sponsor was added.	To comply with request from Health Authority
Section 8.4.3.2 (Paternal exposure)	The outcome for a partner pregnancy was to be followed until 12 weeks (≥5 half-lives) after last dose of IP, instead of 16 weeks (5 half-lives); both durations are longer than the elimination half-life for benralizumab.	To match the duration of the safety follow-up period in this study
Section 9.2 (Sample size determination) and Section 9.4.4 (Methods for multiplicity control)	Multiplicity testing strategy was modified to strongly control for type 1 error rate at 0.05 level.	Based on FDA feedback to SAP
Section 9.4.1.3 (Analysis methods for secondary efficacy variables)	Responder analysis for CAT score and E-RS:COPD total score were added.	To support the meaningfulness of a statistically significant mean change from baseline and to provide additional information for scientific exchange with regard to characterizing meaningful benefits in health status and symptoms
Section 9.4.2 (Safety analyses)	Shift analyses for physical examination findings were removed.	Data will not be collected in such a way to allow this analysis; any abnormal physical examination findings are to be captured as AEs and the eCRF only captures whether or not a physical examination was performed.
Appendix F1 (Anaphylaxis)	Timing for collection of a blood sample to measure serum tryptase was changed from 60 (±30) minutes to 90 (±30) minutes following an exacerbation.	To optimize timing of sample collection for measuring serum tryptase; serum tryptase levels typically reach peak concentration at 1-2 hrs after an exacerbation

Version 2.0, 02 December 2019		
Section # and name	**Description of change**	**Brief rationale for change**
Appendix G	Table of accepted ICS dose formulations was added.	Will serve as a global reference of acceptable ICS doses/formulations to assist sites in determining eligibility for inclusion criterion #7

Version 1.0, 24 April 2019
Initial creation

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

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1 PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Schedule of activities up to Week 56

Study Procedures	Run-in Period [a]			Treatment Period															For early discontinued patients [b]		Details in CSP Section
Visit	1	2 [a]	2.X [a]	3	4	5	6p	7	8p	9	10p	11	12p	13	14p	15	16p	17	IPD	Phone FU	
Week	-5 up to -13	4 wks after V1	if applicable	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	8-12 wks after final IP dose	Phone FU Q4W after IPD	
Visit Window (days)		±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Clinical procedures																					
Informed consent	X [c]																				Appx A 3
Inclusion/exclusion criteria	X	X	X	X																	5.1, 5.2
Medical and COPD history	X																				4.1.2
COPD treatment history	X																				4.1.2
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Smoking status	X			X	X	X		X		X		X		X		X		X	X	X	8.2.4
Complete physical exam	X			X														X	X		8.2.3
Brief physical exam					X	X		X		X		X		X		X					8.2.3
Weight, height	X [d]									X								X	X		8.2.3.1
Vital signs	X	X	X	X	X	X		X		X		X		X		X		X	X		8.2.5
Supplemental oxygen (O_2) status	X	X	X	X	X	X		X		X		X		X		X		X	X	X	8.11.1
CCI		X [e,f]		CCI																	8.11.2

Table 1 Schedule of activities up to Week 56

Study Procedures	Run-in Period [a]			Treatment Period															For early discontinued patients [b]		Details in CSP Section
Visit	**1**	**2 [a]**	**2.X [a]**	**3**	**4**	**5**	**6p**	**7**	**8p**	**9**	**10p**	**11**	**12p**	**13**	**14p**	**15**	**16p**	**17**	**IPD**	**Phone FU**	
Week	**-5 up to -13**	**4 wks after V1**	**if applicable**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**8-12 wks after final IP dose**	**Phone FU Q4W after IPD**	
Visit Window (days)		**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Safety measurements																					
ECG		X								X								X	X		8.2.6
Clinical chemistry	X			X	X	X				X				X				X	X		8.2.1
Hematology, WBC w/ differential [h]	X			X	X	X				X				X				X	X		8.2.1
Urinalysis	X			X	X	X				X				X				X	X		8.2.1
Serology (hepatitis B and C; p24 antigen; HIV-1/2)	X																				8.2.1.1
FSH [i]	X																				8.2.2
Serum pregnancy test in WOCBP	X																				8.2.2
Urine pregnancy test (dipstick) in WOCBP [j]				X	X	X		X		X		X		X		X		X	X		8.2.2
TB test (if applicable)	X [e]																				4.1.2
Pneumococcal/ influenza vaccination, if applicable	X [e]																				8.11.3
AEs				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3

Table 1 Schedule of activities up to Week 56

Study Procedures	Run-in Period [a]			Treatment Period															For early discontinued patients [b]		Details in CSP Section
Visit	**1**	**2 [a]**	**2.X [a]**	**3**	**4**	**5**	**6p**	**7**	**8p**	**9**	**10p**	**11**	**12p**	**13**	**14p**	**15**	**16p**	**17**	**IPD**	**Phone FU**	
Week	**-5 up to -13**	**4 wks after V1**	**if applicable**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**8-12 wks after final IP dose**	**Phone FU Q4W after IPD**	
Visit Window (days)		**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Pharmacologic, genetic, and biomarker assessments																					
PK [k]				X	X	X		X		X				X		X		X	X [l]		8.5
ADA				X				X		X				X		X		X	X [l]		8.9
Serum and whole blood biomarkers				X						X								X [m]			8.8
Blood sampling for genetic analysis (optional)				X																	8.7
Efficacy measurements																					
Spirometry (Pre-BD and Post-BD)	X																				8.1.2
Spirometry (Pre-BD)		X [n]	(X)[n]	X [n]	X	X				X				X				X	X		8.1.2
Acute COPD exacerbation evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1
eDiary dispensed to patient	X																				8.1.3
Patient completes daily eDiary: • EXACT-PRO/ E-RS: COPD • background medication use	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.3.1, 8.1.3.2, 8.1.3.3

Table 1 Schedule of activities up to Week 56

Study Procedures	Run-in Period [a]			Treatment Period															For early discontinued patients [b]		Details in CSP Section
Visit	**1**	**2 [a]**	**2.X [a]**	**3**	**4**	**5**	**6p**	**7**	**8p**	**9**	**10p**	**11**	**12p**	**13**	**14p**	**15**	**16p**	**17**	**IPD**	**Phone FU**	
Week	**-5 up to -13**	**4 wks after V1**	**if applicable**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**8-12 wks after final IP dose**	**Phone FU Q4W after IPD**	
Visit Window (days)		**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
• rescue medication use • symptom severity questionnaire																					, 8.1.3.4
SGRQ, CAT, EQ-5D-5L[o]	X	X [n]	X [n]	X [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.3.5 , 8.1.3.6 , 8.1.3.7
OEQ [p]				X	X	X		X		X		X		X		X					8.1.3.8
Site checks eDiary compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Appendix E
Healthcare resource utilization				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.10
Investigational product (IP) administration																					
Randomization				X																	0, 6.3.1
IP administration				X	X	X		X		X		X		X		X		X [q]			6.1

[a] The duration of the run-in period is flexible and can be extended by up to 13 weeks (91 ±3 days) total, as described in Section 4.1.2. Additional run-in visits (V2.1, V2.2., etc.) will be scheduled in case of extension. Interval between V1 and V2 is 4 weeks (28 ±3, days), and between V2 (or last V2.X) and V3 is 1 week (7 ±3 days). The time between V2 (or last V2.X) and V3 can be extended beyond 7 (+) day, if needed.

[b] Details regarding procedures for patients who discontinue treatment but remain in the study are described in Section 7.1.1, patients lost to follow-up in Section 7.2, and patients who discontinue from the study in Section 7.3.

[c] It is recommended that informed consent is obtained prior to V1 to allow the patient to follow medication restrictions for spirometry. Please refer to Section 8.1.2 (spirometry) for details. Paper or electronic version.

[d] Height will be measured at V1 only.

[e] These procedures can be performed any time during the run-in period after key eligibility criteria (including eosinophil levels and spirometry) have been confirmed. The results must be obtained and assessed prior to randomization. At least 7 days should elapse between vaccination and the first dose of IP.

[f] If CCI is not feasible at V2, chest X-ray may be acceptable (see section 8.11.2). CCI [redacted] should only be performed for participants with a qualified CCI [redacted] No follow-up CCI [redacted] should be performed.

[g] CCI [redacted]
CCI

[h] Eosinophil, basophil, and monocyte counts will be redacted from the central laboratory reports (see Section 6.3.2).

[i] FSH test is done only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for ≥12 months.

[j] A positive urine test (dipstick) result must be confirmed with a serum beta-HCG.

[k] All samples for PK must be taken prior to IP administration.

[l] PK and ADA samples will not be collected after IPD visit in patients who discontinue IP early.

[m] Whole blood should not be collected during Visit 17.

[n] Spirometry and CAT performed at V2 and V2.X will be assessed for variability and the need for run-in extension, as per Section 4.1.2. Spirometry and CAT performed at V3 will be used as a baseline only. After FEV_1 stability is established, additional spirometries are not needed during the run-in period even if extended run-in period is necessary for other reasons.

[o] The SGRQ, CAT, and EQ-5D-5L will be available for completion at run-in visits starting from V1. V3 assessments will be completed at the site before other study procedures. After V3, the patient will complete the assessments at home 28 ±3 days for V4 and every 28 ±7 days for other Visits. If not completed prior to the post-randomization clinic visit, the patient will complete the eDiary assessments at the site prior to other study procedures. Patients with phone follow-up will confirm completion during follow-up phone calls.

[p] OEQ question 1 will be administered 7 ±2 days after the visit. All other OEQ questions will be omitted.

[q] For the last patient having V17 at Week 56 (EOT), no IP administration should occur.

ADA anti-drug antibody; AEs adverse events; BD bronchodilator; CAT COPD assessment tool; COPD chronic obstructive pulmonary disease; CSP Clinical Study Protocol; CCI [redacted]; ECG electrocardiogram; EQ-5D-5L European Quality of Life-5 Dimensions; E-RS:COPD Evaluating Respiratory Symptoms in COPD; EXACT-PRO Exacerbations of Chronic Pulmonary Disease Tool – Patient-reported Outcome; FSH follicle-stimulating hormone; FU follow-up; HCG human chorionic gonadotropin; HIV-1/2 human immunodeficiency virus-1/2; IP investigational product; IPD investigational product discontinuation (visit); OEQ Onset of Effect Questionnaire; p phone visit; PK pharmacokinetics; SAEs serious adverse events; SGRQ St. George's Respiratory Questionnaire; TB tuberculosis; V visit; WBC white blood cell (count); wks weeks; WOCBP women of childbearing potential.

Table 2 Schedule of activities after Week 56

Study Procedures	Treatment period (continued)			Treatment completion	For early discontinued patients		Details in CSP Section
Visit	Phone contact Every 8 weeks starting at Week 60 (V18,20,22…etc)	Treatment visit every 8 weeks [g] (V19, 21, 25…etc)	Treatment visit every 24 weeks (V23, 29, 35…etc)	End Of Treatment (EOT)	IPD	Modified FU	
Week (Wk)	Wk 60, 68, 76 etc.	Wk 64, 72, etc.	Wk 80, 104, etc.	8 wks after the last IP dose	8-12 wks after the last IP dose	Modified FU (on-site/phone) Q4W after IPD	
Visit Window (days)	± 7	± 7	± 7	± 14	± 7	± 7	
Acute COPD exacerbation evaluation	X	X	X	X	X	X	8.1.1
AEs	X	X	X	X	X	Only SAEs, related AEs, and DAEs[f]	8.3
SAEs	X	X	X	X	X	X	8.3
Concomitant medication	X	X	X	X	X	X	6.5
Supplemental oxygen (O_2) status		X	X	X	X	X	8.11.1
Smoking status		X	X	X	X	X	8.2.4
Complete physical exam				X	X		8.2.3
Brief physical exam		X[g]	X				8.2.3
Weight			X	X	X		8.2.3.1
Vital signs		X[g]	X	X	X		8.2.5
ECG			X	X	X		8.2.6
Pre-BD Spirometry			X	X	X		8.1.2
Clinical chemistry			X	X	X		8.2.1
Hematology, WBC w/ differential[a]			X	X	X		8.2.1
Urinalysis			X	X	X		8.2.1

Table 2 Schedule of activities after Week 56

Study Procedures	Treatment period (continued)			Treatment completion	For early discontinued patients		Details in CSP Section
Visit	Phone contact Every 8 weeks starting at Week 60 (V18,20,22…etc)	Treatment visit every 8 weeks [g] (V19, 21, 25…etc)	Treatment visit every 24 weeks (V23, 29, 35…etc)	End Of Treatment (EOT)	IPD	Modified FU	
Week (Wk)	Wk 60, 68, 76 etc.	Wk 64, 72, etc.	Wk 80, 104, etc.	8 wks after the last IP dose	8-12 wks after the last IP dose	Modified FU (on-site/phone) Q4W after IPD	
Visit Window (days)	± 7	± 7	± 7	± 14	± 7	± 7	
Urine pregnancy test (dipstick) in WOCBP[b]		X [g]	X	X	X		8.2.2
PK[c]			X		X		8.5
ADA			X		X		8.9
Healthcare resource utilization	X	X	X	X	X		8.10
Patient completes daily eDiary: - background medication use - rescue medication use - symptom severity questionnaire	X	X	X	X [e]	X [e]		8.1.3.2, 8.1.3.3, 8.1.3.4
SGRQ, CAT, EQ-5D-5L (every 24 weeks on eDiary)[d]			X	X [e]	X [e]		8.1.3.5, 8.1.3.6, 8.1.3.7
Site checks eDiary compliance		X	X	X	X		Appendix E
Annual influenza vaccine (if applicable)	Annual						8.11.3
IP administration		X	X				6.1

[a] Eosinophil, basophil, and monocyte counts will be redacted from the central laboratory reports (see Section 6.3.2).

[b] A positive urine test (dipstick) result must be confirmed with a serum beta-HCG prior to administration of IP.

[c] All samples for PK must be taken prior to IP administration.

[d] If not completed prior to the clinic visit, the patient will complete these eDiary assessments at the site prior to other study procedures. Patients with phone follow-up will confirm completion during follow-up phone calls.

[e] Patients will return eDiary at EOT visit or at IPD visit if they discontinue IP early.

[f] In the Modified study Follow-up (MFU), following the IPD visit through study completion, only SAEs, related AEs, and DAEs will be collected. Ongoing AEs from Treatment period will continue to be followed.

[g] If the patient opts for self-administration, these visits can be performed remotely (i.e., telephone/ telemedicine contact). In such cases, the brief physical examination and vital signs assessments may be skipped. For details on pregnancy testing in case of remote visits, refer to section 8.2.2.

ADA anti-drug antibody; AEs adverse events; BD bronchodilator; CAT COPD assessment tool; COPD chronic obstructive pulmonary disease; CSP Clinical Study Protocol; DAEs adverse events leading to discontinuation; ECG electrocardiogram; EOT End of treatment (visit); EQ-5D-5L European Quality of Life-5 Dimensions; FU follow up; HCG human chorionic gonadotropin; IP investigational product; IPD investigational product discontinuation (visit); PK pharmacokinetics; Q4W every 4 weeks; SAEs serious adverse events; SGRQ St. George's Respiratory Questionnaire; V Visit; Wk Week; WBC white blood cell (count); WOCBP women of childbearing potential.

1.2 Synopsis

International co-ordinating investigator

PPD
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Protocol Title: 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 (RESOLUTE)

Short Title: Efficacy and Safety of Benralizumab in Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) with a History of Frequent Exacerbations

Rationale:

Benralizumab is a humanized, afucosylated, monoclonal antibody that binds specifically to the human interleukin-5 (IL-5) receptor alpha subunit (IL-5Rα) on the target cell and directly depletes eosinophils through antibody-dependent cell-mediated cytotoxicity. The mechanism of action of benralizumab makes it a potential treatment option for the high unmet need in chronic obstructive pulmonary disease (COPD) patients with eosinophilic inflammation and at risk for exacerbations.

Benralizumab is being developed as an add-on maintenance treatment and for the prevention of exacerbations in patients with COPD. This Phase 3 study will evaluate the efficacy and safety of benralizumab in patients with moderate to very severe COPD with elevated peripheral blood eosinophils and a history of frequent COPD exacerbations despite receiving triple (inhaled corticosteroid/long-acting β2 agonist/long-acting muscarinic antagonist [ICS/LABA/LAMA]) background therapy.

Table 3 Study objectives

Primary Objective:	Endpoints/Variables:
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: • Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids; and/or • Use of antibiotics; and/or • An inpatient hospitalization or death due to COPD
Secondary Objectives:	**Endpoints/Variables:**
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] and domain scores • 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 [a] at the study site
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	Annual rate of hospitalizations due to COPD; Length of hospital stay; ICU days; annual rate of hospitalizations and emergency department visits combined due to COPD; annual rate of unscheduled outpatient visits, including unscheduled visits to study sites due to COPD; and annual rate of unscheduled healthcare encounters due to COPD
To evaluate the pharmacokinetics and immunogenicity of benralizumab in this patient population	• Serum benralizumab concentration • Anti-benralizumab antibodies

Table 3 Study objectives

Safety Objectives:	Endpoints/Variables:
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 Assessments related to AEs cover • Occurrence/frequency • Relationship to IP as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP Other significant AEs
Exploratory Objectives:	**Endpoints/Variables:**
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 100 mg 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 100 mg 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 and whole blood biomarkers [b]	Serum protein biomarkers CCI
To collect and store CCI from voluntary patient samples for exploratory CCI analyses [b]	A CCI sample for CCI will be collected from patients who have consented to participate in the exploratory CCI analyses component of the study

Table 3 Study objectives

To evaluate the effect of benralizumab 100 mg on CCI CCI CCI	Change from baseline in: • CCI CCI • CCI CCI • CCI CCI • CCI • CCI

[a] Key secondary efficacy endpoints

[b] Results for these exploratory objectives may be reported outside the Clinical Study Report.

CAT COPD assessment tool; COPD chronic obstructive pulmonary disease; CCI ; DLCO diffusion capacity of the lung for carbon monoxide; EQ-5D-5L European Quality of Life-5 Dimensions; E-RS:COPD Evaluating Respiratory Symptoms in COPD; EXACT-PRO Exacerbations of Chronic Pulmonary Disease Tool – Patient-reported Outcome; IC inspiratory capacity; ICU intensive care unit; IP investigational product; PCR polymerase chain reaction; RV residual volume; SGRQ St. George's Respiratory Questionnaire.

Overall design:

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, 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 (thereafter 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 stable triple (ICS/LABA/LAMA) background therapy for at least 3 months and ICS-based dual inhaled treatment for the remainder of the year. 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 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 Section 4.1.3. The primary endpoint will be analyzed 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 enrollment throughout the run-in and treatment period. Background inhaled

medications may be provided/reimbursed by AstraZeneca 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.

Study Period:

Estimated date of the first patient enrolled is Q3 2019.

Estimated date of last patient completed is Q2 2025.

Number of Patients:

A total of 642 patients are expected to be randomized in the study at a 1:1 ratio to either benralizumab 100 mg SC or matching placebo treatment groups.

Treatments and treatment duration:

Once enrolled, patients will enter a run-in period with a minimum duration of 5 weeks that can be extended up to 13 weeks. Following the run-in period, patients confirmed to be eligible will be randomized in a 1:1 ratio to receive benralizumab 100 mg or placebo SC 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. When the end-of-treatment (EOT) visit has been identified for the last patient (i.e. V17), all patients' final visits will be scheduled. The study will end when all patients complete their final visit.

The investigational product (IP) will be administered SC as a single injection via an accessorized prefilled syringe (APFS). No dose changes are allowed. If a patient presents with a condition that contraindicates dosing, administration of IP will be withheld and resumed as soon as the condition resolves. All patients, regardless of whether they remain on IP treatment or not, will be encouraged to remain in the study and be followed to study completion (see Section 7.1.1).

Statistical methods

Efficacy analyses will be performed using the full analysis set (FAS), which will include all patients randomized who receive at least 1 dose of IP, irrespective of their protocol adherence and continued participation in the study, according to the Intent-to-Treat principle.

The primary efficacy endpoint is the annualized rate of moderate and severe COPD exacerbations over the first 56 weeks. 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 is included, regardless of whether a patient remains on blinded IP or not.

The primary endpoint will be assessed first in the primary population (patients with ≥3 exacerbations in the previous year) and then assessed on the overall population of patients with ≥2 exacerbations in the previous year. Exacerbation rate in the benralizumab 100 mg group will be compared to the exacerbation rate in the placebo group using a negative binomial model. The response variable in the model will be the number of COPD exacerbations over the first 56 weeks of the treatment period. The model will include covariates of treatment group, region, and number of exacerbations in the previous year. The logarithm of the follow-up time during the first 56 weeks will be used as an offset variable in the model. Hypothesis testing for the primary analysis will be performed at the 2-sided 5% significance level.

Annualized rate of COPD exacerbations leading to hospitalization or death (i.e. severe exacerbations) will be analyzed through EOT using a similar negative binomial model as outlined for the primary efficacy variable.

Unless otherwise noted, all secondary efficacy endpoints will be analyzed in patients with a history of ≥3 exacerbations in the previous year and repeated in patients with a history of ≥2 exacerbations in the previous year using data up to Week 56. 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 through EOT.

The study will recruit patients on triple (ICS/LABA/LAMA) background therapy with screening 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.

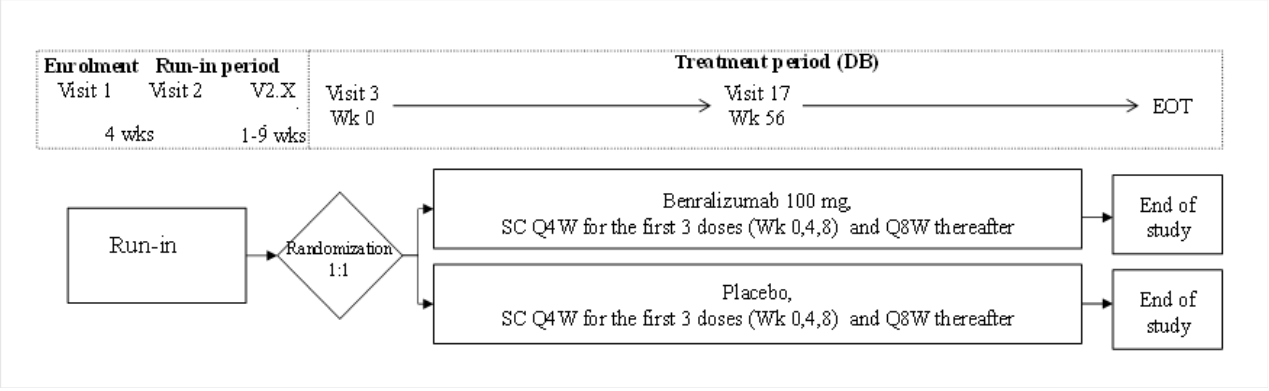
For the primary endpoint of annualized exacerbation rate over the first 56 weeks, a minimum of 225 patients/arm with ≥3 exacerbations in the previous year (450 total) will be randomized to achieve at least 90% power to detect a 30% reduction in benralizumab 100 mg versus placebo. This calculation assumes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

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 (approximately 192 patients) to characterize efficacy in patients with ≥2 exacerbations in the previous year.

1.3 Schema

The general study design is summarized in Figure 1.

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, as described in Section 4.1.2. Additional run-in visits (Visits 2.1, 2.2, etc.) will be scheduled in case of extension.

Week 56: Primary endpoint (annual 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 (i.e. V17), 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.

2 INTRODUCTION

Benralizumab is a humanized, afucosylated, monoclonal antibody that binds specifically to the human interleukin-5 (IL-5) receptor alpha subunit (IL-5Rα) on the target cell and directly depletes eosinophils through antibody-dependent cell-mediated cytotoxicity. The mechanism of action of benralizumab makes it a potential treatment option for the high unmet need in chronic obstructive pulmonary disease (COPD) patients with eosinophilic inflammation and at risk for exacerbations.

Benralizumab is being developed as an add-on maintenance treatment and for prevention of exacerbations in patients with COPD. The benralizumab COPD clinical program consists of a Phase 2a study (identified as MI-CP196), followed by two Phase 3 studies (identified as GALATHEA [D3251C00003] and TERRANOVA [D3251C00004]) that evaluated benralizumab in patients with moderate to very severe COPD with a history of exacerbations despite standard maintenance therapy with inhaled corticosteroid/long-acting β2 agonist (ICS/LABA), long-acting muscarinic antagonist (LAMA)/LABA (double) or ICS/LABA/LAMA (triple) across a range of baseline blood eosinophils.

2.1 Study rationale

The two previous Phase 3 studies of benralizumab, GALATHEA, and TERRANOVA, in patients with moderate to very severe COPD and a history of exacerbations despite standard of care with double or triple background therapy did not meet the primary endpoint of annualized exacerbation rate. These studies evaluated benralizumab doses of 10 mg (TERRANOVA only), 30 mg, and 100 mg. Consistent and meaningful reductions in annualized exacerbation rates over placebo were observed with the 100 mg dose in both studies; further details provided in Section 4.2. Prospective exploratory analyses of GALATHEA and TERRANOVA identified a subpopulation more likely to experience improvement with benralizumab: a patient with elevated peripheral blood eosinophils and frequent COPD exacerbations in the previous year despite being optimized on triple (ICS/LABA/LAMA) background therapy. The purpose of this Phase 3 study is to confirm the efficacy of benralizumab 100 mg in patients with moderate to very severe COPD, these characteristics represent patients most likely to benefit from benralizumab treatment.

In order to avoid bias, this study will be randomized and double-blinded. A placebo group will be included to ensure a control for comparison effects.

2.2 Background

Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and mortality and is projected to be the third-leading cause of death and disability worldwide by 2020 (Global Initiative for Chronic Obstructive Lung Disease [GOLD 2013]).

Acute exacerbations of COPD (AECOPD) are responsible for much of the morbidity and mortality from COPD and are responsible for a large portion of the economic burden of COPD. An AECOPD is defined as a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations that are acute in onset and necessitates a change in regular medication in a patient with underlying COPD (Rodriquez-Roisin 2000). A Spanish study suggests that frequent exacerbations are associated with increased mortality at 5 years, and ≥3 exacerbations in the first year were associated with a 4-fold increase in risk (Soler-Cataluna et al 2005). One small study suggests patients with moderate to severe COPD and frequent exacerbations may experience a more rapid decline in lung function as compared to patients with infrequent exacerbations (Donaldson et al 2002).

Increasing evidence has accumulated in recent years to support the role of eosinophilic inflammation in COPD. Airway and sputum eosinophilia have been associated with exacerbations of COPD (Saetta et al 1994, Bafadhel et al 2011). Blood eosinophil levels are associated with COPD exacerbations and likely predict corticosteroid therapy. Several studies have shown a relationship between sputum eosinophils and blood eosinophils in COPD patients indicating higher blood eosinophils may be a surrogate for eosinophilic inflammation of the airway (Hastie et al 2017; Negewo et al 2016; Bafadhel et al 2011; Kolsum et al 2017). Post-hoc analyses of previous COPD studies indicated that up to 40% of COPD patients have blood eosinophilia and that patients with elevated blood eosinophils experienced greater reduction of exacerbations from ICS-containing therapy (Singh et al 2014, Pavord et al 2016, Pascoe et al 2015, Siddiqui et al 2015, Vedel-Krogh et al 2016). Management strategies aimed at reducing eosinophilic airway inflammation using ICS or oral corticosteroids (OCS) are associated with decreased exacerbation frequency (Brightling et al 2000; Pizzichini et al 1998; Siva et al 2007; Bafadhel et al 2011). These data have influenced the latest GOLD strategy for treatment of COPD patients where it is now recommended that in patients with blood eosinophils ≥300 cells/μL and at risk of exacerbations, ICS should be added to combination bronchodilator therapy (GOLD 2019). This suggests a mechanistic link between blood eosinophils, exacerbations, and ICS responsiveness.

These data suggest blood and airway eosinophils may be used to help identify COPD patients most likely to respond to corticosteroid therapy but also imply that therapies specifically targeting eosinophils in COPD patients with elevated blood or airway eosinophils may have beneficial effects. Furthermore, not all patients with eosinophilic inflammation associated with COPD will respond adequately to corticosteroids, particularly inhaled corticosteroids, and may require additional therapies to achieve improved clinical benefit. Despite adequate treatment with inhaled triple background therapy, approximately 30% to 40% of patients continue to have moderate or severe exacerbations (Pavord et al 2017). Therefore, options are limited for patients who are on standard of care and still experiencing severe exacerbations of COPD.

A recent Phase 3 study of mepolizumab, a serum neutralizing antibody against IL−5 showed a statistically significant 18% reduction over placebo in COPD exacerbations in patients with elevated eosinophils on triple background therapy. A second Phase 3 mepolizumab study of a similar design had a similar magnitude of effect but failed to meet statistical significance, possibly due to being underpowered (Pavord et al 2017). Two Phase 3 studies of benralizumab, GALATHEA and TERRANOVA, showed meaningful trends in moderate and severe exacerbation reductions in specific subgroups receiving 100 mg doses of benralizumab. The magnitude of reduction seen in GALATHEA for the 100mg dose was similar to that observed for mepolizumab in COPD patients.

A detailed description of the chemistry, pharmacology, efficacy, and safety of benralizumab is provided in the Investigator's Brochure.

2.3 Benefit/risk assessment

In order to evaluate the clinical benefit/risk balance for benralizumab, preclinical and clinical data have been taken into consideration, as well as a review of the available information for monoclonal antibodies that are approved for and are in development for the treatment of COPD. Benefits of benralizumab over placebo include clinically significant reductions in annual exacerbation rate and annual severe exacerbation rate.

Benralizumab has been well tolerated, with the most frequently observed adverse events (AEs) from the Phase 3 controlled studies being generally reflective of a moderate to very severe COPD patient population.

Potential risks of benralizumab are as follows:

- Serious infections have been reported for benralizumab. A relationship between eosinophil depletion and serious infection has not been established.
- Malignancies have been reported at a low incidence in the completed and ongoing studies of benralizumab. Eosinophils have been found in association with solid tumors, especially tumors of epithelial origin (breast and colon) and may play an active role in tumor defense by modulating host defenses, or may be a bystander effect. However, the cause and consequences (i.e. pro-tumorigenic versus anti-tumorigenic) of eosinophil recruitment and accumulation into tumors are unclear (Jacobsen et al 2012). Risk minimization measures include exclusion of patients with active or recent malignancy and routine pharmacovigilance activities.
- Cardiovascular disease is a common co-morbidity of COPD and could be manifested as major adverse cardiovascular events (MACE). MACE events were low and balanced across treatment groups in the previous Phase 3 studies in COPD patients.
- Serious hypersensitivity reactions (including anaphylaxis) are an identified risk of biologic therapy, including benralizumab. Anaphylaxis may be life-threatening. Risk minimization includes an observation in line with clinical practice following IP administration for the appearance of any acute drug reactions.

- Development of anti-drug antibodies (ADA) to benralizumab has been documented. Theoretical risks of developing ADA may include decreased drug efficacy and hypersensitivity reactions (e.g. anaphylaxis or immune complex disease). There was no apparent impact of ADA on overall benralizumab safety or efficacy in the previous Phase 3 studies in COPD patients.
- Eosinophils are a prominent feature of the inflammatory response to helminthic parasitic infections. Therefore, there is a theoretical risk that prolonged eosinophil depletion may diminish the ability to defend against helminthic parasites. Risk minimization measures include exclusion of patients with an untreated parasitic infection, in conjunction with the performance of routine pharmacovigilance activities.

The ionising radiation from low dose computed tomography (CT) or chest X-ray may cause a small increase in the risk of developing cancer. Participants will be informed of the risks associated with CT before entering the study, and not every participant in the study will receive a CT scan during the study (Section 8.11.2). In keeping with the ALARA concept (As Low as Reasonably Achievable), the trial uses optimised CT scan protocols, using the lowest possible radiation dose for each participant in order to provide acceptable image quality for the quantitative measurements performed in the study. For more detailed information related to CT radiation dose, imaging risks, and best imaging practices, please refer to the study Radiology Manual.

The benefit/risk assessment for benralizumab in moderate to very severe COPD patients based on early clinical development through Phase 3 appears favorable. Risk minimization measures include the exclusion of patients with allergy or reaction to any component of the IP formulation, untreated helminth parasitic infection, and active or recent malignancy, in conjunction with the performance of routine pharmacovigilance activities.

More detailed information about the known and expected benefits and risks and safety profile of benralizumab may be found in the Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Table 4 Study objectives

Primary Objective:	Endpoints/Variables:
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: • Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids; and/or • Use of antibiotics; and/or • An inpatient hospitalization or death due to COPD
Secondary Objectives:	**Endpoints/Variables:**
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] and domain scores • 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 [a] at the study site
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	Annual rate of hospitalizations due to COPD; Length of hospital stay; ICU days; annual rate of hospitalizations and emergency department visits combined due to COPD; annual rate of unscheduled outpatient visits including unscheduled visits to study sites due to COPD; and annual rate of unscheduled healthcare encounters due to COPD

Table 4 Study objectives

To evaluate the pharmacokinetics and immunogenicity of benralizumab in this patient population	• Serum benralizumab concentration • Anti-benralizumab antibodies
Safety Objectives:	**Endpoints/Variables:**
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 Assessments related to AEs cover • Occurrence/frequency • Relationship to IP as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP Other significant AEs
Exploratory Objectives:	**Endpoints/Variables:**
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 and whole blood biomarkers [b]	Serum protein biomarkers CCI [redacted]
To collect and store CCI from voluntary patient samples for exploratory CCI analyses [b]	A CCI sample for CCI will be collected from patients who have consented to participate in the exploratory CCI analyses component of the study

Table 4 Study objectives

To evaluate the effect of benralizumab 100 mg on CCI CCI CCI	Change from baseline in: • CCI CCI • CCI CCI • CCI CCI • CCI • CCI

[a] Key secondary efficacy endpoints

[b] Results for these exploratory objectives may be reported outside of the Clinical Study Report.

CAT COPD assessment tool; COPD chronic obstructive pulmonary disease; CCI
DLCO diffusion capacity of the lung for carbon monoxide; EQ-5D-5L European Quality of Life-5 Dimensions; E-RS:COPD Evaluating Respiratory Symptoms in COPD; EXACT-PRO Exacerbations of Chronic Pulmonary Disease Tool – Patient-reported Outcome; IC inspiratory capacity; ICU intensive care unit; IP investigational product; PCR polymerase chain reaction; RV residual volume; SGRQ St. George's Respiratory Questionnaire.

4 STUDY DESIGN

4.1 Overall design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, 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 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 Section 0. The primary endpoint will be analyzed at Week 56.

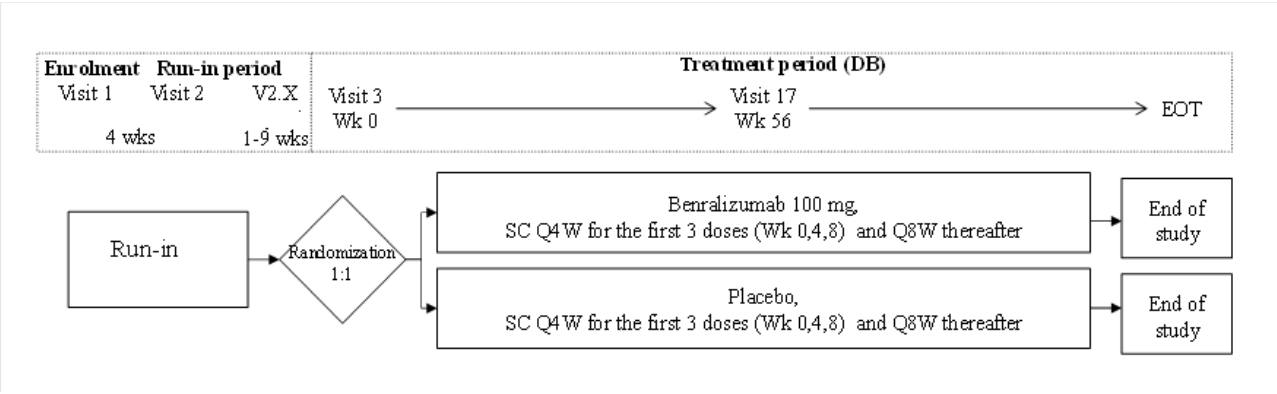
At randomization, patients will be stratified by country and number of exacerbations in the previous year (2 or ≥3). Randomization to the stratum of 2 exacerbations in the previous year will be capped to ensure ≥70% of patients with ≥3 exacerbations in the previous year in the study population. Patients will be maintained on triple (ICS/LABA/LAMA) background

therapy, from enrollment 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. For details on treatments given during the study, see Section 6.1 Treatments Administered. For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

Figure 2 Study design



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

Week 56: Primary endpoint (annual 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 (ie, V17), 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.

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

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (e.g., during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby

compromising the study site staff or the patient's ability to conduct the study. The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

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

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

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the Informed Consent Form (ICF) should be signed as soon as feasible i.e. at the patient's next visit).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.
- Home Visit or Visit in Remote Location: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home Investigational Product (IP) administration: Performed by a site qualified HCP, HCP provided by a TPV, or by the patients or the patient's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

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

4.1.2 Run-in Period (enrollment up to randomization)

Duration of run-in period

The minimum duration of the run-in period is 35 (±3) days (i.e., 5 weeks) with a flexible duration that can be extended up to 91 (±3) days (i.e., approximately 13 weeks) in total to allow time to address eDiary and background therapy compliance issues, monitor clinical stability in case of acute events, monitor symptom variability, etc. as detailed in the criteria listed below. Extension of the run-in period beyond 13 weeks can be allowed if deemed necessary by the investigator and agreed with the AZ study physician/delegate (e.g., in case of acute events or need to obtain additional evidence of the patient's eligibility).

Visit 2 should occur 28 (±3) days (i.e., 4 weeks) after Visit 1, followed by the randomization visit (Week 0) in 7 (±3) days (i.e. 1 week). If the run-in period is extended, additional run-in visits (Visit 2.1, 2.2, etc.), usually with a 4-week interval will be scheduled to re-assess

eligibility and confirm whether the patient can proceed to randomization, should continue in extended run-in, or should be excluded from the study. The time between Visit 2 (or last Visit 2.X) and Visit 3 can be extended beyond 7 (+3) days, if needed. Specific scenarios for extending the run-in period are described below. Screen failure procedures are described in Section 5.4.

The run-in period may be extended for the following reasons:

- eDiary compliance issues:
  - Patient has difficulties with eDiary entries and is unable to demonstrate the required level of compliance with eDiary completion (see inclusion criterion 13, Section 5.1) and may need additional instruction on eDiary.[1]
  - Patient demonstrates <70% compliance with triple (ICS/LABA/LAMA) background therapy during the entire run-in period based on the eDiary records (see inclusion criterion 14, Section 5.1).[1]
- To allow adequate time for recovery and/or stabilization in case of certain events that may occur during the run-in, e.g.:
  - If patient experiences a COPD exacerbation during the screening period, at least 2 weeks should elapse between the treatment end date (e.g. last dose of systemic corticosteroids treatment and/or antibiotics and/or end of hospitalization, whichever is later) and the next run-in visit prior to randomization. A longer recovery period might be necessary to ensure complete patient recovery or for eosinophils to return to pre-systemic steroid levels for eligibility purposes.
  - In the case of pneumonia during run-in, at least 6 weeks should elapse between the event end date (e.g. last dose of systemic corticosteroids and/or antibiotics treatment and/or end of hospitalization, whichever is later) and the next run-in visit prior to randomization. A longer recovery period might be necessary to ensure full patient recovery or for eosinophils to return to pre-systemic steroid levels for eligibility purposes.
  - Minor changes of formulation of a patient's background inhaled medication, e.g., change of individual component (e.g. fluticasone propionate to budesonide at equivalent dose) or switch between devices (e.g. budesonide/formoterol to fluticasone propionate/salmeterol) are allowed as long as the patient remains on ICS/LABA/LAMA with an acceptable ICS dose, see Section 6.5.1). The patient should be stable on the new treatment regimen for at least 4 weeks prior to randomization (see inclusion criterion 7, Section 5.1).

[1] In case of handheld device issues or required Patient re-training, the compliance period re-starts after device issue solution or re-training performed. Minimum 2 weeks period is required to confirm Patient's compliance.

- If the patient was previously on a chronic antibiotic, but is no longer taking it, at least 6 weeks should elapse between the last dose of antibiotic and randomization (see exclusion criterion 25, Section 5.2).

- Patients with a significant change (>3 points in either direction) in CAT score during the run-in period have to continue in extended run-in for at least 4 additional weeks to further monitor CAT score variability; and cannot proceed to randomization without consultation and agreement with AZ study physician/delegate (see inclusion criterion 15, Section 5.1).
- Patients who exhibit unexpectedly high variability of FEV_1 during the run-in period, defined as a change in FEV_1 >400 mL and/or >25% in either direction have to continue in extended run-in for at least 4 additional weeks for additional evaluation for etiology of variability, necessary follow-up actions, and assessment of continued patient eligibility. These patients cannot proceed to randomization without consultation and agreement with AZ study physician/delegate.
- Additional time required to confirm patient eligibility, e.g. to perform necessary assessments, obtain medical documentation, etc.
- Other reasons to be discussed with AZ study physician.

Enrollment

Each potential patient will provide written informed consent prior to any study-specific procedures. It is recommended that informed consent is obtained prior to Visit 1 to allow the patient to follow medication restrictions for spirometry; refer to Section 8.1.2 for details. The patient's enrollment should be registered in an Interactive Web Response System (IWRS) on the day the informed consent form (ICF) is signed.

Following the registration of a patient and assignment of an enrollment code, the screening procedures will be initiated to assess the study eligibility criteria (see Table 1).

In case of a recent COPD exacerbation and/or lower respiratory tract infection and/or use of systemic corticosteroids for any reason, it is recommended that Visit 1 procedures are postponed by 6 weeks after the last dose of systemic corticosteroid treatment to allow the eosinophils to return to the pre-systemic steroid levels and the total recovery from the event.

Visit 1

Visit 1 is primarily focused on screening assessments, e.g. confirmation of COPD diagnosis, history of exacerbations and maintenance treatment for COPD (including compliance in the previous year), lung function (spirometry) parameters, and measurement of blood eosinophil levels. Relevant information regarding past medical and surgical history, comorbidities, concomitant medications, and smoking history will be collected.

The complete list of Visit 1 procedures is provided in Table 1. If any screening assessments are re-scheduled, it is important that the results are received and evaluated prior to the next scheduled visit.

Visit 1 procedures may be split, if needed, for example, to obtain an initial central eosinophil count before proceeding with other screening assessments. If Visit 1 is split, it is recommended to complete all the procedures within the next 7 days. It is important that patients have at least 2 spirometry and CAT assessments 4 weeks (±3 days) apart during the run-in to assess for variability. Run-in period may be extended and additional visits scheduled to meet this requirement.

Documented evidence of eligibility

Records of historical physician-diagnosed COPD, COPD exacerbation(s) in the previous year, and ICS/LABA/LAMA use (Section 5.1, inclusion criteria 5, 6, and 7) are required source documentation. A patient's verbal history suggestive of COPD symptoms and/or COPD exacerbation(s) in the previous year, but without supporting documentation, is not sufficient to satisfy these inclusion criteria. The definition of a qualifying COPD exacerbation is provided in inclusion criterion 6, Section 5.1.

Examples of acceptable documentation for:

- COPD disease state and COPD exacerbation(s) in the previous year:
  - Clinic visit (primary or specialist healthcare provider [HCP]) notes or emergency room/hospital records listing COPD as a current diagnosis and providing evidence of ≥2 moderate or severe exacerbations in the previous year (52 weeks prior to enrollment)
  - Documented prescription of systemic corticosteroids of at least 3 days duration (or 1 injection of depot formulation) for treatment of COPD exacerbation
  - Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a subject was hospitalized or treated with systemic corticosteroids for a COPD exacerbation
- Use of triple (ICS/LABA/LAMA) therapy for at least 3 months immediately prior to enrolment (including assessment of patient's compliance and any identified gaps in treatment or periods of double/monotherapy):
  - Recent, active medication list as per a HCP note
  - Filled prescriptions based on a pharmacy record
  - Another acceptable medical record as per local clinical practice
  - Signed and dated notes from a treating/referring physician, including information regarding COPD diagnosis and treatment of an exacerbation with systemic corticosteroids or antibiotics

COPD characteristics and history

Additional information on respiratory disease history and COPD characteristics will be collected and recorded in the electronic case report form (eCRF). This will include assessment for chronic bronchitis criteria (chronic cough and mucus production for ≥3 months in 2 successive years) and/or current/past radiographic evidence (chest radiograph or CT scan) of emphysema.

Historical eosinophil value

Information about historical blood eosinophil values (highest absolute value of eosinophils in the year prior to enrollment) will be obtained and must be supported by respective source documentation. In cases where a patient has no documented historical eosinophil count, the patient must have 2 eosinophil tests performed (at least 4 weeks apart) during the run-in period; one value must be ≥300/µL and the other must be ≥150/µL to meet the eligibility criteria.

Central laboratory eosinophil count

Central laboratory tests for absolute blood eosinophil count will be performed at Visit 1 (refer to Table 1 for details). Patients who have a blood eosinophil count of <300 but ≥150/µL at Visit 1 can be re-tested at Visit 2 or an unscheduled visit. It is recommended that re-tests due to low blood eosinophil count are performed not earlier than 4 weeks from the previous testing. Patients with a test result for blood eosinophil count of <150/µL during the run-in period will be screen failed.

Spirometry

Spirometry assessment will be performed to evaluate whether lung function meets the study eligibility criteria. Patients who are unable to produce acceptable post-bronchodilator spirometry data at Visit 1 may be re-tested at an additional (unscheduled) screening visit. If a patient is unable to meet medication restrictions for spirometry at Visit 1 (see Section 6.5.4.1), it is recommended that spirometry assessment is re-scheduled and performed as soon as feasible but no later than at Visit 2. If spirometry is postponed for more than 7 days from Visit 1, Visit 2 will be re-scheduled (or an additional Visit 2.X performed) to allow at least 4 weeks (±3 days) between the spirometry visits to assess for variability.

TB test and vaccination

If applicable, tuberculosis (TB) test will be performed according to the local standard of care as determined by local guidelines. Patients should receive a pneumococcal vaccination (or a booster, if required) if the patient has not been previously vaccinated unless contraindicated. Influenza vaccination should be given if it is the autumn or winter period and repeated annually, provided these vaccinations are not up to date (see Section 8.11.3).

Patients on chronic antibiotics treatment
Patients who received ≥6 months of antibiotics treatment in the previous year must have a hearing assessment within 3 months prior to enrollment or during the run-in period. These patients must be interviewed for potential hearing issues/tinnitus at enrollment; any reported issues will be recorded as part of medical history.

eDiary
Each patient will be dispensed an electronic handheld device, i.e. eDiary, at Visit 1 to record symptoms and medication use and to complete PRO questionnaires (see Section 8.1.3).

Visit 2

Visit 2 is primarily designed for evaluation of eligibility assessments results, eDiary compliance, and follow up on any significant changes in patient's symptoms and lung function (i.e., CAT and FEV_1 variability). By the end of this visit the investigator is expected to decide whether the patient can proceed to the randomization visit or will stay in an extended run-in period. Any concerns regarding patient's eligibility should be discussed with AZ study physician/delegate.

The complete list of Visit 2 procedures is provided in Table 1.

Spirometry
Pre-bronchodilator Spirometry assessment at Visit 2 (and, if necessary, at additional run-in visits, e.g. Visits 2.1, 2.2, etc) will be performed to assess for lung function variability. Patients who exhibit unexpectedly high variability of FEV_1 during the run-in period, defined as a change in FEV_1 >400 mL and/or >25% in either direction, will continue in extended run-in for at least 4 additional weeks for additional evaluation of the etiology of variability, necessary follow-up actions, and assessment of continued patient eligibility. These patients cannot proceed to randomization without consultation and agreement with AZ study physician/delegate (see "Duration of run-in period" at the beginning of Section 4.1.2).

Patients with established FEV_1 stability do not need additional spirometry tests, even if additional run-in visits are needed due to other reasons.

Chest computed tomography (CT) or chest X-ray

Patients who cannot provide a CT dated within 6 months prior to enrollment, will be scheduled for a baseline CT at Visit 2/2.X or as soon as key eligibility criteria have been confirmed (see Section 8.11.2). This assessment may be re-scheduled within the run-in period as needed; however, the results (i.e. clinical interpretation by a Radiologist or a Physician qualified to read and interpret radiological chest examination per local standard practice) must be obtained and assessed locally prior to randomization to inform exclusion criterion 3.

If neither historical nor screening CT can be obtained (e.g. in case of clinical contraindications, access issues, or patient's refusal), a historical chest X-ray performed within 6 months prior to enrollment or during the run-in period will be acceptable to inform exclusion criterion 3.

4.1.3 Treatment period (randomization to EOT)

The final assessment of the patient's eligibility must be performed at the latest run-in visit (Visit 2/2.X) prior to randomization. This includes evaluating all inclusion/exclusion criteria, run-in period assessment results (see Section 4.1.2), and compliance with triple (ICS/LABA/LAMA) background therapy and eDiary completion.

Visit 3 should start with the confirmation of the patient's eligibility based on previous assessment results and evaluation of any ongoing AEs or COPD exacerbation(s) to decide whether the patient may proceed with the Visit 3 procedures and randomization transaction in IWRS.

Patients confirmed to be eligible will undergo Visit 3 assessments listed in Table 1 and will be randomized in a 1:1 ratio to receive benralizumab 100 mg or placebo every 4 weeks for the first 3 doses and then Q8W thereafter. The first dose of IP will be administered at Week 0 after the patient's randomization via an IWRS. 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 (i.e. V17), then the final visits for all patients will be scheduled. The study will end when all patients complete their final visit.

Patients will attend scheduled clinic visits at 4-week intervals up to Week 8 and then at 8-week intervals up to the EOT visit to complete protocol-specific assessments listed in Table 1 and Table 2. If the Patient chooses the self-administration, the Site Visits will occur every 24 weeks after V17. Telephone visits will occur between clinic visits at 8-week intervals starting at Week 12 as per the study plan (Table 1 and Table 2). Unscheduled visits may be initiated as needed, and assessments performed at these visits are at the investigator's discretion. Note changes in the schedule of activities after Week 56 (see Table 1 and Table 2).

Patients will be maintained on triple (ICS/LABA/LAMA) background therapy throughout the treatment period. In case of a COPD worsening/exacerbation (see Section 8.1.1), patients should be evaluated at the study site at an unscheduled visit, when feasible, or a scheduled visit, if the worsening happens to fall within a scheduled visit window.

Patients will record their COPD symptoms and responses to the questionnaires using the eDiary throughout the treatment period (see Section 8.1.3 for details). Patients will return the eDiary at the EOT visit.

To reduce patient burden and to allow flexibility, patients will have the option of at-home or remote location self-administration of IP or at-home or remote location administration of IP by the patient's caregiver using the accessorized prefilled syringe (APFS) after Week 56. Refer to protocol Section 6.1.2 for details.

Patients who prematurely discontinue from IP should return to the study site within a recommended window of 8 to 12 weeks after the last dose of IP and complete procedures described for the IP discontinuation (IPD) visit (see Section 7.1.1). Discontinued patients will continue in the study follow-up until the last patient has the opportunity to complete a minimum of 56 weeks. At that point, all patients will complete the study.

Completion or early discontinuation of IP will be registered via IWRS for each patient.

4.2 Scientific rationale for study design

The study population was identified based on the findings from the previous Phase 3 studies of benralizumab in patients with moderate to very severe COPD, GALATHEA, and TERRANOVA. The two Phase 3 studies were of nearly identical study design and included patients with a history of exacerbations despite double or triple background therapy with ICS/LABA, LAMA/LABA or ICS/LAMA/LABA across a range of baseline blood eosinophils. The primary population was patients with a baseline eosinophil count ≥220/μL.

In the primary analysis, the benralizumab 100 mg dose resulted in a 17% and a 7% reduction over placebo in the primary endpoint of annual COPD exacerbation (moderate and severe combined) rate in GALATHEA and TERRANOVA, respectively. However, clinically relevant reductions in severe exacerbations (defined as exacerbations leading to hospitalization or death) were observed in both studies with the greatest effect observed in the benralizumab 100 mg group (43% and 32% for GALATHEA and TERRANOVA, respectively).

Pre-planned analyses evaluated specific subpopulations and resulted in the following:

- Patients on triple (ICS/LABA/LAMA) background therapy (approximately 70% and 60% of patients in GALATHEA and TERRANOVA, respectively) had a consistent treatment effect on annual COPD exacerbation rate with benralizumab 100 mg in both studies: 18% and a 17% reduction over placebo, respectively.
- Patients with more frequent exacerbations in the previous year (≥3 versus ≤2) had a greater treatment effect on annual COPD exacerbation rate and annual severe exacerbation rate with benralizumab 100 mg.
- No treatment effect was observed on annual COPD exacerbation rate in patients with a baseline blood eosinophil count <220/μL.

Findings in these subpopulations were consistent across the studies and supported by pooled analyses. Taken together, these characteristics identify those patients most likely to benefit from benralizumab treatment.

An eosinophil cut point of ≥300/µL is used for this study. In the previous GALATHEA and TERRANOVA studies, no efficacy was seen in patients with low eosinophil counts (<220/µL). The treatment response was similar between patients with ≥220/µL and ≥300/µL. GOLD 2019 references a 300 cells/µL threshold in terms of response to ICS and a 300/µL cutoff is more practical from a clinical perspective and aligns with clinical laboratory blood cell count data resolution.

A history of frequent exacerbations in the previous year (≥3) was the strongest and most consistent predictor of treatment response in GALATHEA and TERRANOVA, therefore, this study will be powered for the primary population of patients with ≥3 exacerbations in the previous year. Study enrollment is expanded to also include patients with 2 exacerbations in the previous year to allow further exploration in a broader population (patients with ≥2 exacerbations in the previous year) given that there was evidence of a treatment effect in this subset of patients on triple (ICS/LABA/LAMA) background therapy with a baseline blood eosinophil count ≥220/µL in the GALATHEA and TERRANOVA studies. In a pooled post hoc analysis in this population (blood eosinophils ≥220/µL, ≥2 exacerbations in the previous year, on triple therapy), benralizumab 100 mg treatment resulted in a 20% reduction over placebo in the annual exacerbation rate and a 55% reduction over placebo in the annual severe exacerbation rate.

Chest CT imaging will be included in the study in order to provide needed information related to exclusion criterion 3 CCI [redacted]
CCI [redacted]

4.3 Justification for dose

In the previous Phase 3 studies, GALATHEA and TERRANOVA, long-term treatment with benralizumab 10, 30, or 100 mg Q8W through Week 48 was well tolerated in patients with moderate to very severe COPD. There were no appreciable differences in the safety results across the 3 dose groups.

The results from both studies provided consistent and clear evidence of a greater treatment effect for the benralizumab 100 mg dose over the 30 mg dose in reducing the annual rate of COPD exacerbations (moderate and severe combined) and severe exacerbations, as well as all other exacerbation endpoints, in patients with a baseline blood eosinophil count ≥220/µL. The benralizumab 10 mg dose (TERRANOVA only) provided inconsistent results compared with the 100 mg dose across exacerbation endpoints. However, for severe exacerbations, a greater treatment effect was observed for the benralizumab 100 mg dose compared with the

10 mg dose (32% and 25% reduction over placebo, respectively) in patients with a baseline blood eosinophil count ≥220/μL. In patients with more frequent prior exacerbations (≥3 exacerbations in the previous year) and a baseline blood eosinophil count ≥220/μL, a much greater treatment effect for the benralizumab 100 mg dose over the 10 mg dose was apparent for COPD exacerbations (moderate and severe combined; 23% vs 9% reduction over placebo, respectively) as well as for severe exacerbations (34% vs 17% reduction over placebo).

Considering the more consistent findings of efficacy, particularly in the subpopulation with more frequent previous exacerbations and elevated eosinophils (≥220/μL), the benralizumab 100 mg dose was chosen for this study.

4.4 End of study definition

For the purpose of Clinical Trial Transparency (CTT) the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA.

See Appendix A 5 for guidelines on the dissemination of study results.

5 STUDY POPULATION

Approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomized to a study intervention. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures, refer to Section 5.4.

In this protocol, "enrolled" patients are defined as those who sign informed consent. "Randomized" patients are defined as those who undergo randomization and receive a randomization number.

Procedures for withdrawal of incorrectly enrolled patients are described in Section 7.1.2.

5.1 Inclusion criteria

Informed consent

1 Provision of signed and dated ICF prior to any mandatory study-specific procedures, sampling, and analyses.

The ICF process is described in Appendix A 3.

Age and Sex

2 Patient must be 40 to 85 years of age inclusive, at the time of signing the ICF.

3 Male and/or female.

Type of patient and disease characteristics

4 Current smoker or ex-smoker with a tobacco history of ≥10 pack-years (1 pack-year = 20 cigarettes smoked per day for 1 year). (*Note:* electronic cigarette [e-cigarette] use does not contribute to the pack-year count for eligibility.)

5 History of moderate to very severe COPD with a post-bronchodilator FEV_1/forced vital capacity (FVC)<0.70 and a post-bronchodilator FEV_1 ≤65% of predicted normal value at screening central spirometry assessment.

6 Documented history of 2 or more moderate and/or severe COPD exacerbations[1][2] that required treatment with systemic corticosteroids (at least 3 days or a single depot formulation injection) and/or hospitalization within 52 weeks prior to enrollment.

[1] An exacerbation will be considered moderate if it required treatment with systemic corticosteroids and did not result in hospitalization. An exacerbation will be considered severe if it resulted in hospitalization.
[2] A minimum 7-day interval is required between the end of treatment (last dose of systemic corticosteroid or antibiotics or the last day of hospitalization) of one exacerbation to the treatment start of the next exacerbation.

(a) Exacerbations treated with antibiotics alone are not considered as meeting the criterion unless it is accompanied by treatment with systemic corticosteroids and/or hospitalization.

(b) Hospitalization is defined as an inpatient admission ≥24 hours in the hospital, in an observation area, the emergency department, or other equivalent healthcare facility depending on the country and healthcare system.

(c) Previous exacerbations should be confirmed to have occurred while the patient was on stable double or triple (ICS/LABA/LAMA) background therapy for COPD and not as a result of a gap or step down in the treatment.

(d) At least one qualifying COPD exacerbation should occur while on stable uninterrupted triple therapy prior to enrolment.

7 Documented use of triple (ICS/LABA/LAMA[1]) background therapy for COPD for ≥3 months immediately prior to enrollment.

(a) Treatment with at least double inhaled therapy containing ICS (e.g. ICS/LABA or ICS/LAMA) for the remaining of 52 weeks prior to enrolment. Use of LABA/LAMA is allowed if ICS cannot be tolerated.

(b) ICS in a dose approved for COPD or equivalent to ≥250 mcg of fluticasone propionate daily.[2]

(c) Patient could have switched therapies during the previous year and/or stepped down for short periods of time, although the total cumulative duration that the patient was not using inhaled double or triple background therapy must not exceed 2 months.

(d) Patient must be on stable therapy/doses for the last 3 months prior to randomization. (Individual component changes or switches between devices are allowed as long as the patient remains on ICS/LABA/LAMA with an acceptable ICS dose)

8 Blood eosinophil count ≥300/µL at screening central laboratory testing, supported by at least 1 documented historical blood eosinophil count of ≥150/µL within 52 weeks of enrollment. In the absence of historical data, an additional blood eosinophil count must be obtained by repeating the testing during the run-in period (at least 4 weeks apart).

9 CAT total score ≥15 at Visit 1 (also see inclusion criterion 15).

[1] SAMA taken at regularly scheduled intervals (every 6-8 hours or at least 3 times daily) will be considered equivalent to LAMA.

[2] Appendix G provides a list of alternative ICS prescribed in different markets as part of combinations therapy for COPD that are equivalent to a total daily medium dose of fluticasone propionate (≥250 mcg).

Reproduction

10 Negative pregnancy test (serum) for female patients of childbearing potential at Visit 1 (enrollment).

11 Women of childbearing potential (WOCBP) must agree to use a highly effective method of birth control (confirmed by the investigator) from enrollment throughout the study duration and within 12 weeks after last dose of IP. Highly effective forms of birth control (those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation- oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation- oral, injectable, or implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Sexual abstinence, i.e. refraining from heterosexual intercourse (The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.)
- Vasectomized sexual partner (provided that partner is the sole sexual partner of the WOCBP study patient and that the vasectomized partner has received medical assessment of the surgical success)

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

- Women <50 years old will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle-stimulating hormone (FSH) levels in the postmenopausal range. Until FSH is documented to be within menopausal range, treat the patient as WOCBP.
- Women ≥50 years old will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.

Additional eligibility criteria

12 Ability to read, write, and use electronic devices. Please refer to Appendix E for details.

Additional eligibility criteria to be confirmed prior to randomization (at the last run-in visit):

13 Compliance with eDiary completion during the run-in period, defined as at least 8 fully completed daily diary assessments in the 14-day period prior to randomization visit (i.e. Study Days -14 to -1).

14 At least 70% compliance with the patient's triple (ICS/LABA/LAMA) background therapy (defined as taking all maintenance medication as scheduled for the day) during the run-in period based on the eDiary records.[1]

15 CAT score ≥15 at the last run-in visit prior to randomization and stable within ±3 points variance compared to previous visits. If a patient demonstrates significant change (>3 points in either direction) in CAT score during the run-in period, randomization must not occur without agreement with AZ study physician/delegate, and the run-in period must be extended for an additional 4 weeks.

5.2 Exclusion criteria

Medical conditions

1 Clinically important pulmonary disease other than COPD (e.g. active lung infection, clinically significant bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia).

2 Current diagnosis of asthma, according to the Global Initiative for Asthma (GINA) or other accepted guidelines, prior history of asthma, or asthma-COPD overlap according to GINA/GOLD[2]. Childhood history of asthma is allowed and defined as asthma diagnosed and resolved (i.e. not requiring the use of any maintenance or rescue medication) before the age of 18.

3 Radiological findings suggestive of a respiratory disease other than COPD that is contributing to the patient's respiratory symptoms. Radiological findings of solitary pulmonary nodules without appropriate follow up and demonstration of stability as per standard of care or results suggestive of acute infection.

[1] In case of handheld device malfunction or required Patient re-training, the compliance period re-starts after device issue solution or re-training performed. Minimum 14-day period prior to randomization visit is required to confirm Patient's compliance.
[2] Patients with an existing diagnosis of asthma-COPD overlap must be evaluated by the investigator to determine if patient meets exclusion for asthma-COPD overlap based on GINA/GOLD.

4 Another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts (e.g. allergic bronchopulmonary aspergillosis/mycosis, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome).

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

- Affect the safety of the patient throughout the study
- Influence the findings of the study or their interpretation
- Impede the patient's ability to complete the entire duration of the study

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

7 Signs and/or symptoms of cor pulmonale and/or right ventricular failure.

8 Patients receiving long-term treatment with oxygen >4.0 liters/minute (L/min). While breathing supplemental oxygen, patients should demonstrate an oxyhemoglobin saturation ≥89%. In order to be admitted to the study, patients on long-term oxygen therapy have to be ambulatory and be able to attend clinic visits.

9 Use, or need for chronic use, of any non-invasive positive pressure ventilation device (NIPPV). *Note*: Patients using continuous positive airway pressure (CPAP) for Sleep Apnea Syndrome are allowed in the study.

10 History of known immunodeficiency disorder including a positive test for human immunodeficiency virus, HIV-1 or HIV-2.

11 Active liver disease. Chronic stable hepatitis B and C (including positive testing for hepatitis B surface antigen or hepatitis C antibody), or other stable chronic liver disease are acceptable if patient otherwise meets eligibility criteria. Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice, or cirrhosis.

12 Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥3 times the upper limit of normal (ULN), confirmed by repeated testing[1] during the run-in period. Transient increase of AST/ALT level that resolves by the time of randomization is

[1] If an AST or ALT test is ≥3xULN, testing should be repeated during the run-in period at least 1 week apart.

acceptable if, in the investigator's opinion, the patient does not have an active liver disease and meets other eligibility criteria.

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

14 History of alcohol or drug abuse within the past year, which may compromise the study data interpretation as judged by investigator or AZ study physician.

15 Malignancy, current or within the past 5 years, except for adequately treated non-invasive basal cell and squamous cell carcinoma of the skin and cervical carcinoma-in-situ treated with apparent success more than 1 year prior to Visit 1. Suspected malignancy or undefined neoplasms.

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

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

18 Patients with a history of surgical or endoscopic (e.g. valves) lung volume reduction within the 6 months prior to enrollment. Patients with a history of partial or total lung resection (single lobe or segmentectomy is acceptable).

19 Scheduled major surgical procedure during the course of the study. Minor elective procedures are allowed.

20 History of anaphylaxis to any biologic therapy or vaccine.

Prior/concomitant therapy

21 Receipt of blood products or immunoglobulins within 30 days prior to randomization.

22 Receipt of marketed or investigational biologic product within 4 months or 5 half-lives prior to randomization, whichever is longer. Exception: Patients on stable therapy for 3 months before randomization who intend to stay on treatment throughout the study with marketed biologic products that are not likely to interfere with the safety assessment and/or efficacy of benralizumab, for example, for the treatment of osteoporosis, migraine,

pain, diabetes, obesity, ocular, cardiovascular, or metabolic diseases, can participate in the study.[1]

23 Receipt of live attenuated vaccines 30 days prior to randomization.

24 Chronic use of immunosuppressive medication (including but not limited to: methotrexate, troleandomycin, cyclosporine, azathioprine, rectal corticosteroids, and systemic corticosteroids) or expected need for chronic use during the study.

25 Chronic use of antibiotics[2] if the duration of treatment is <9 months prior to randomization (Week 0). Chronic macrolide or other antibiotic therapy is allowed provided the patient has been on a stable dose/regimen for ≥9 months prior to randomization and has had ≥2 COPD exacerbations while on stable therapy. If the patient was previously on chronic antibiotic but is no longer taking it, the patient cannot be randomized until 6 weeks after the last dose.[3]

Prior/concurrent clinical study experience

26 Receipt of any investigational non-biologic product within 30 days or 5 half-lives prior to enrollment, whichever is longer.

27 Receipt of benralizumab within 12 months prior to enrollment.

28 Known history of allergy or reaction to any component of the IP formulation.

Other exclusions

29 Donation of blood, plasma, or platelets within the past 90 days prior to enrollment.

30 Pregnant, breastfeeding, or lactating women.

31 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

32 Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements.

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[1] Examples not limited to: Teriparatide, Denosumab, Romosozumab, CGRP-antagonist, GLP-1 agonists, GLP-1 receptor agonists, Tenecteplase, Reteplase, PCSK9 inhibitors, recombinant botulinum neurotoxin, recombinant erythropoietin, VEGF inhibitors for ocular diseases, recombinant urate oxidase, and other recombinant enzymes.
[2] Patients who received ≥6 months of antibiotics treatment in the previous year must have a hearing assessment within 3 months prior to enrollment or during the run-in. These patients must be interviewed for potential hearing issues/tinnitus at enrollment; any reported issues will be recorded as part of medical history.

[3] Washout period for antibiotics taken for conditions not associated with respiratory such as: surgical prophylaxis, dental procedures might be shortened upon the discussion with AZ study physician.

5.3 Lifestyle restrictions

Restrictions on strenuous exertion and dietary considerations are required prior to spirometry measurements, as described in Section 8.1.2.

Women of childbearing potential must use highly effective contraceptive methods from enrollment throughout the study and for at least 12 weeks (≥5 half-lives) after last administration of the IP, as stated in inclusion criterion 11, Section 5.1.

Patients must abstain from donating blood, plasma, or platelets from the time of informed consent and for 12 weeks (≥5 half-lives) after last dose of IP.

5.4 Screen failures

Screen failures are defined as patients who signed the ICF to participate in the clinical study but are not subsequently randomly assigned to IP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). These patients should have the reason for study withdrawal recorded in the eCRF as 'Screen failure' (i.e. patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

This study includes a flexible run-in period that can be extended in order to address potential issues during the run-in period; refer to Section 4.1.2 for circumstances that may warrant extension of the run-in period. If the patient ultimately does not meet all inclusion criteria or meets any of the exclusion criteria, the patient should be screen failed using an IWRS.

Individuals who do not meet criteria for participation in this study (screen failure) may be re-screened once without additional approval from the AZ study physician if the patient did not meet one of the inclusion criteria (4-15) unless there was a significant protocol issue during the first run-in/screening period. Ex: significant non-compliance with study procedures, among others.

Patients who screen fail due to an exclusion criteria (16-32) and other cases will be considered extraordinary and need discussion/approval case by case with the AZ study physician.

In case of re-screening, all medical events that have occurred since the first enrollment will be recorded as part of medical history, and all the screening procedures will be repeated (exception to be discussed with AZ study physician/delegate). Re-screened patients should be assigned the same patient number as for the initial screening. Re-screening will be documented so that its effect on study results, if any, can be assessed.

6 STUDY TREATMENTS

Study treatment is defined as any investigational product (including marketed product comparator and placebo) or medical device intended to be administered to a patient according to the study protocol. Study treatment in this study refers to benralizumab or placebo.

6.1 Treatments administered

Descriptions of the study treatments are provided in Table 5. Benralizumab and placebo administered in the study will be a clear to opalescent, colourless to yellow solution.

Table 5 Study treatments

	Treatment 1	**Treatment 2**
Study treatment name:	Benralizumab	Placebo
Dosage formulation:	100 mg/mL solution for injection in accessorized prefilled syringe (APFS), 1 mL fill volume	Matching placebo solution for injection in APFS, 1 mL fill volume
Route of administration	Subcutaneous (SC)	SC
Dosing instructions:	Benralizumab active solution will be administered SC to the patients using an APFS. Refer to Section 6.2.	Placebo solution will be administered SC to the patients using an APFS. Refer to Section 6.2.
Packaging and labelling	Study treatment will be provided in APFS. Each syringe will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement. The labels will be translated into local languages where applicable and required by local regulations.	Study treatment will be provided in APFS. Each syringe will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. The labels will be translated into local languages where applicable and required by local regulations.
Provider	AstraZeneca	AstraZeneca

Before IP administration

All applicable visit procedures, including sample collection, should be completed prior to IP administration. If the patient cannot tolerate particular visit procedure during the visit (e.g. spirometry), IP can be administered, and the procedure should be re-scheduled for a different date, preferably within the visit window. No procedures should be performed after the dosing on the day of IP administration. Pharmacokinetic (PK) and ADA samples must always be collected before IP administration.

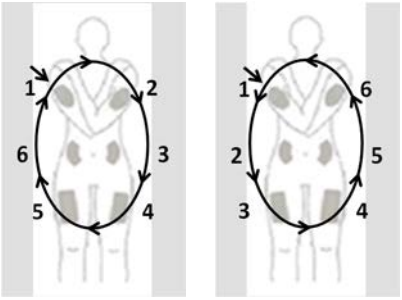
Prior to each IP administration:

- WOCBP should have the urine pregnancy test performed before IP administration. IP will be administered only when the result of the test is negative (see Section 8.2.2) .
- Investigator/authorized delegate will evaluate the patient's condition for potential contraindications for dosing (see Section 6.1.1).
- Investigator/authorized delegate will evaluate the injection site as per standards of medical care.

IP administration

The IP will be administered subcutaneously as a single injection via the APFS. It is advised that the site of injection of IP is rotated such that the patient receives IP at a different anatomical site at each treatment visit. Suggested injection site rotation sequence is presented below (see Figure 3). The injection site should be documented in the source at each treatment visit and recorded in the eCRF.

Figure 3 Injection sites and examples of rotation scheme



If rotation of the injection site is not realized, the reason for this should be documented in the source.

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

After IP administration at the study site, the patient should be observed for potential acute drug reactions in line with clinical practice. When a remote visit is performed for self-administration, we encourage the investigator or qualified designee to contact the patient after the dose administration and check for the possibility of acute reactions in line with clinical practice.

6.1.1 IP administration re-scheduling

Every effort should be taken to keep IP administration within the visit window.

If a patient presents with a condition that contraindicates dosing, IP will be withheld and administered as soon as possible when the contraindicating condition resolves.

IP should not be administered, and the dosing is to be re-scheduled in the presence of the following conditions:

- An intercurrent illness that, in the opinion of the investigator, may compromise the safety of the patient.
- Any event or laboratory abnormality that, in the opinion of the investigator or the sponsor, contraindicates dosing or could result in complications.

It is recommended that the AZ study physician/delegate be contacted in case of any questions.

If IP cannot be administered at a scheduled treatment visit (e.g. due to conditions listed above), it can be postponed as necessary and administered as soon as possible.

When IP dosing needs to be postponed, it is recommended that all scheduled treatment visit procedures (except for IP administration) are still performed within the visit window.

Re-scheduled IP dose can be then administered at an unscheduled visit. Physical exam and vital signs assessment are the minimum procedures to be performed at this visit. For WOCBP, the urine pregnancy test must be performed; IP will be administered only when the result of the test is negative (see Section 8.2.2). It may also include remaining visit procedures (not performed at the scheduled visit) and additional assessments as deemed necessary by the investigator.

If the visit procedures cannot be conducted within the window (e.g. the patient is unable to attend the study site), then the entire visit will be re-scheduled along with IP dose.

If a dose is significantly delayed it is recommended to keep at least 2 weeks interval before the next dose. If a postponed dose overlaps with the next treatment visit window, the postponed dose will be skipped, and the next dose of IP given at the regularly scheduled visit. The visit schedule will be always calculated from randomization visit date.

If the patient misses 2 consecutive or non-consecutive doses of IP[1] within a calendar year, it is strongly recommended that the site discuss with AZ study physician to review the patient's adherence to treatment and decide on the patient's disposition.

Discontinuation procedures are described in Section 7.1.1. All patients, whether they remain on IP or not, will be encouraged to stay in the study and followed until the study completion.

[1] A ‘missed’ dose is a dose not administered until the next treatment visit window.

6.1.2 Optional Self-Administration of Investigational Product

To reduce patient burden and allow flexibility after Week 56 of the study, the patients will have an option for self-administration of IP using the APFS by the patient or their caregiver. The Investigator must evaluate the patient and/or their caregiver to ensure they are capable of performing the IP self-administration and provide them with appropriate training. All necessary supplies and instructions for administration and documentation of IP administration will be provided.

After week 56, some visits do not include extensive on-site assessments and can optionally be performed as remote visits through telephone/telemedicine contact (see Table 2, on-clinic visits every 8 weeks) for patients who opted for IP self-administration. IP kits and urine dipsticks for pregnancy testing (for WOCBP) for the remote visits may be dispensed starting from Visit 17 (week 56) as described in Study Instructions for Self-Administration of Investigational Product by the Patient and/or their Caregiver in RESOLUTE study. After week 56 mandatory on-site visits will occur at 24-week (6-month) intervals, and patients may be dispensed IP kits and pregnancy tests to perform self-administration in between.

If the IP is self-administered by the patient/ caregiver, IP should be administered on a day of scheduled visit after all visit assessments are completed.

The Investigator or qualified designee will conduct a telemedicine contact on the day of the visit prior to IP self-administration to confirm that the patient does not have any contraindications for IP dosing. WOCBP will be asked about any concerns for pregnancy and will be advised to perform a urine pregnancy test.

If the urine pregnancy test result is positive, the patient should contact the site and should not administer IP. Site personnel will provide the patient with further instructions.

It is strongly recommended that the patient is contacted by the investigator or qualified designee after the dose is administered, to evaluate for any potential acute reactions, in line with clinical practice. Any AEs reported by the patient should be recorded in source documents and entered in the eCRF.

Refer to the Study Instructions for Self-Administration of Investigational Product by the Patient and/or their Caregiver in RESOLUTE study for step-by-step guidance including Investigator assessment/training of patient and/or caregiver and drug accountability.

The option of self- administration of IP will only be available in countries where allowed according to local regulations.

6.2 Preparation/handling/storage/accountability

The IP will be administered at the study site, on treatment visits, and within visit windows as specified in the schedule in Table 1 and Table 2. After Week 56, IP may be administered within the treatment window as described in Table 2, either on-site by an HCP or, optionally, self-administered by the patient or caregiver. Self-administration of the IP requires assessment and training by the Investigator (Section 6.1.2).

IP will be supplied to the site in a kit with an APFS of either benralizumab or placebo. Each kit will have a unique ID that is printed on all labels within the kit (i.e. the outer carton label and the label of each container within the carton).

All shipments of IP include a data logger which will allow the investigator, or designee, to confirm that appropriate temperature conditions have been maintained during transit for all IP received. Any discrepancies must be reported and resolved before use of the IP.

Only patients enrolled in the study may receive IP and only authorized site staff or trained patient/caregiver may supply or administer IP. At the site, all IP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area, in the original outer container. The IP must be kept under conditions specified on the label (between 2 to 8°C [36 to 46°F], protected from light), with access limited to the investigator and authorized site staff. The temperature should be monitored on a daily basis and documented in the temperature monitoring log.

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

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

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

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IP accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).

An AstraZeneca site monitor will account for all IP received at the site, for unused IP, and for appropriate destruction of unused study treatments. Any unused kits will be destroyed locally (for further details, refer to the Pharmacy Manual). Documentation of IP delivery and destruction should be maintained according to applicable AstraZeneca and institution procedures.

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual (provided to the sites).

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Methods for assigning treatment groups

All patients will be locally assigned to randomized IP using an IWRS. Randomization codes will be assigned strictly sequentially in each stratum as patients become eligible for randomization. Patients will be stratified by country and number of exacerbations in the previous year (2 and or ≥3). Randomization will be capped for the stratum of 2 exacerbations in the previous year to ensure that the study population contains ≥70% of patients with ≥3 exacerbations in the previous year. Eligibility for either stratum is dependent upon documentation for each exacerbation. In order to be eligible for the 2 or ≥3 historical exacerbations stratum, patients must have a respective documented history of 2 or ≥3 moderate and/or severe COPD exacerbations in the previous year that meet the criteria outlined in inclusion criterion 6, Section 5.1; examples of acceptable documentation are provided in Section 4.1.2. Instructions for withdrawing patients from the study after a stratum is closed are provided in Section 7.3.2.

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

If a patient withdraws from the study after randomization, then his/her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

6.3.2 Methods for ensuring blinding

This is a double-blind study in which benralizumab and placebo are not visually distinct from each other. All packaging and labelling of the IP will be done in such a way as to ensure blinding for all sponsor and investigational site staff. Neither the patient nor any of the investigators or sponsor staff who are involved in the treatment, clinical evaluation, and monitoring of the patients will be aware of the treatment received. Since benralizumab and placebo are not visually distinct, IP will be handled by an appropriately qualified member of the study team (e.g. pharmacist, investigator or qualified designee) at the site.

An AstraZeneca site monitor will perform IP accountability. In the event that the treatment allocation for a patient becomes known to the investigator or other study staff involved in the management of study patients, or needs to be known to treat an individual patient for an AE, the sponsor must be notified immediately by the investigator and, if possible, before unblinding.

The following personnel will have access to the randomization list during the study, prior to database lock:

- Those carrying out the packaging and labelling of IP
- Those generating the randomization list
- The AstraZeneca Supply Chain department

The information in the randomization list will be kept from other personnel involved in the conduct of the study in a secure location until the end of the study. No other member of the extended study team at AstraZeneca, or any Contract Research Organization handling data, will have access to the randomization scheme during the conduct of the study.

Maintaining the blind to the patient's blood eosinophil counts

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

- Hematology will be run by the central laboratory. Post-randomization (starting from Visit 3), eosinophil and basophil counts will be redacted from the full hematology reports sent back to the investigative sites. Because complete knowledge of the remaining cell types could permit deduction of the 'eosinophil + basophil' compartment, monocyte counts will also be redacted from the reports.
- If the investigator orders any local safety laboratory assessments, the requested tests should be restricted to the question at hand. For example, if hemoglobin is desired, the investigator should avoid ordering a complete blood cell count with a differential count.
- In cases where the investigator requires an eosinophil, basophil, or monocyte count for managing safety issues, he/she may order these tests as per regular site practice. AstraZeneca should be notified of all such cases.
- Site staff who are directly involved in the patient's management should remain blinded to any eosinophil, basophil, and monocyte results included as part of an outside laboratory report or electronic medical record. To help ensure this, each investigational site will designate an individual (e.g. administrator or another ancillary person) not directly involved in patient management, to receive and blind any eosinophil, basophil, and monocyte results prior to the report being handed over to the site staff involved in the patient's management and prior to filing the laboratory report as a source document. Similarly, eosinophil, basophil, and monocyte results must be redacted from all communications with the sponsor.

6.3.3 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) from the IWRS. Routines for this will be described in the IWRS user manual that will be provided to each site.

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

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

6.4 Treatment compliance

The IP will be administered SC on treatment visits and within visit windows as specified in Table 1 and Table 2. Any change from the dosing schedule, dose interruptions, or dose discontinuations must be recorded in the eCRF; dose modifications are prohibited.

6.5 Concomitant therapy

Investigator/authorized delegate will collect and record information about concomitant medications in the eCRF:

- All background COPD medications (e.g. ICS/LABA/LAMA, chronic antibiotics, etc.) and treatment given for COPD exacerbations in the 12 months prior to enrollment
- All other medications taken for any reason in the 3 months prior to enrollment
- Concomitant treatments given during the study, with reason for the treatment (at each study visit)

COPD medications taken at the time of historical exacerbations, including any recent changes in these medications relative to the timing of the exacerbation, are to be captured in the eCRF.

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

6.5.1 Background (maintenance) medication

Patients must be on stable ICS/LABA/LAMA therapy/doses for the last 3 months immediately prior to enrollment (see inclusion criterion 7, Section 5.1) and during the course of the study, with ICS dose approved for COPD or equivalent to ≥250 mcg of fluticasone propionate daily (see Appendix G for alternative ICS with dose equivalents). All patients are required to be treated with at least double inhaled therapy containing ICS (e.g. ICS/LABA or ICS/LAMA) for COPD for the remainder of the 52 weeks prior to enrolment.

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

Minor changes of formulation of a patient's background inhaled medication, e.g. change of individual component (e.g. fluticasone propionate to budesonide at equivalent dose) or switch between devices (e.g. budesonide/formoterol to fluticasone propionate/salmeterol) are allowed as long as the patient remains on ICS/LABA/LAMA with an acceptable ICS dose. In case of such minor changes, the patient should be stable on the new treatment regimen for at least 4 weeks prior to randomization.

Changes to the patient's background therapy are discouraged during the study, unless judged medically necessary by the investigator. The justification and rationale for treatment changes should be documented in the source notes.

For patients who discontinue IP and will continue in Modified Follow-up (i.e. after Week 56) (see Section 7.1.1), changes to the patient's background therapy may be allowed, if judged medically necessary by the investigator.

During the study, inhaled background medications that are given once daily should be administered in the morning to conform to spirometry measurement requirements.

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

Background medication is not regarded as IP, but may be provided by AstraZeneca according to local regulations, in order to maintain access to these concomitant therapies from enrollment and throughout the duration of the study until the patient completes or withdrawals.

6.5.2 Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

It is recommended that medications to treat a COPD exacerbation are not used for more than 14 days. Recent data suggest that treatment with systemic corticosteroids for shorter periods of time results in similar outcomes with less systemic steroid exposure (Leuppi et al 2013).

6.5.3 Rescue medication

Short-acting β2-agonists (SABAs, e.g. salbutamol, albuterol, terbutaline, levalbuterol), short-acting muscarinic antagonists (SAMA), SABA/SAMA combination or alternative rescue medication, as per local standard of care, may be used during the study in the event of worsening of COPD symptoms.

6.5.4 Restrictions

The restrictions that apply during the study are summarized in Table 6.

Table 6 Allowed, restricted, and prohibited concomitant medication

Unless specifically indicated, all conditions apply from enrollment throughout the study duration. The restrictions below may be waived for patients who have discontinued IP and are in Modified study follow-up (MFU) after Week 56 if the treatment is considered medically necessary by the investigator. Medications not listed in this table are allowed.

Medication	Allowed/Restricted/ Prohibited	Details
Background (maintenance) COPD medication: **triple** (ICS/LABA/LAMA)	**Allowed**	Patients should have evidence of having been treated with triple (ICS/LABA/LAMA) background therapy for COPD for ≥3 months immediately prior to Visit 1 and have to be consistently treated with COPD medications on acceptable doses* throughout the study. Triple background therapy components may be used in fixed-dose combination(s) or separate devices. Nebulized ICS (e.g. budesonide) and/or LABA are accepted as part of maintenance therapy. *ICS dose should be approved for COPD or equivalent to ≥250 mcg fluticasone propionate (see Appendix G for alternative ICS with dose equivalents).
SABA (short-acting β2-agonists, e.g. salbutamol, albuterol, terbutaline levalbuterol)	**Allowed** as rescue medication and for treatment of acute COPD exacerbation	Prophylactic use of SABA in the absence of symptoms is discouraged. However, if deemed necessary by the patient and investigator (e.g. prior to planned exercise), it can be used, but prophylactic inhalations should not be recorded in the daily eDiary, such use should be

Table 6 Allowed, restricted, and prohibited concomitant medication

Unless specifically indicated, all conditions apply from enrollment throughout the study duration.
The restrictions below may be waived for patients who have discontinued IP and are in Modified study follow-up (MFU) after Week 56 if the treatment is considered medically necessary by the investigator. Medications not listed in this table are allowed.

Medication	Allowed/Restricted/ Prohibited	Details
		documented in the medical notes and recorded in the eCRF.
SAMA (short-acting muscarinic antagonists = short-acting anticholinergics; e.g. ipratropium bromide, metered dose inhaler or nebulized)	**Allowed**	SAMA taken at regularly scheduled intervals (q 6-8 hours or at a minimum frequency of 3 times daily) will be considered equivalent to maintenance treatment with LAMA. Rescue use is allowed. It is important that dose regimen is accurately recorded in eCRF (scheduled dose vs. PRN).
Systemic corticosteroids (tablets, suspension, or injections)	**Restricted**	Allowed for treatment of COPD exacerbation. Allowed for treatment of an AE where there is no alternative treatment available, for the duration of <4 weeks. If longer treatment is required, this should be discussed with the AZ study physician to decide on the patient's disposition. Disallowed within 2 weeks prior to randomization and for other reasons throughout the study. Please refer to section 4.1.2 for additional guidance regarding the treatment of pneumonia during the run-in period and washout required before the patient's enrolment.
Other immunosuppressive medication (including but not limited to: methotrexate, troleandomycin, cyclosporine, azathioprine)	**Restricted**	Allowed for treatment of an AE where there is no alternative treatment available for the duration of <4 weeks. If longer treatment is required, this should be discussed with the AZ study physician to decide on the patient's disposition. Disallowed within 4 weeks prior to randomization and for other reasons throughout the study.
Antibiotics	**Restricted**	Allowed to treat COPD exacerbations and/or AEs. Chronic use (>3wks) and use for the prevention of COPD exacerbations is disallowed, unless the patient is on stable dose and regimen for ≥9 months prior to randomization and has had ≥2 COPD exacerbations while on stable therapy (see exclusion criterion 25, Section 5.2).
Antitussives and mucolytics	**Allowed**	
Dermal topical steroids, nasal steroids, topical	**Allowed**	

Table 6 Allowed, restricted, and prohibited concomitant medication

Unless specifically indicated, all conditions apply from enrollment throughout the study duration.
The restrictions below may be waived for patients who have discontinued IP and are in Modified study follow-up (MFU) after Week 56 if the treatment is considered medically necessary by the investigator. Medications not listed in this table are allowed.

Medication	Allowed/Restricted/ Prohibited	Details
ophthalmic and otic corticosteroids		
Antihistamines and ephedrine containing medications	**Allowed**	
PDE4 inhibitors (eg Roflumilast)	**Allowed**	
Xanthines	**Restricted**	Allowed in a dose equivalent to theophylline ≤400mg q day. For doses greater than 400 mg, the dose has to be stable and blood levels should be confirmed to be ≤12 mg/dL, within 8 weeks prior to enrollment or during screening. Blood levels >12 mg/dL should be managed according to local standards of care and the investigator's judgment and discussed with AZ study physician. It is recommended that additional increments in dose are evaluated with blood levels.
Marketed biologics	**Restricted**	Patients on marketed biologic products are allowed in the trial, provided they are compliant with the exclusion criterion 22. During the study, the initiation of marketed biologic product is generally disallowed, except for the treatment of co-morbidities for which no alternative treatment is available. The introduction of any marketed biologic product, that is not likely to interfere with the assessment of safety and/or efficacy of benralizumab, for example, for the chronic treatment of osteoporosis, migraine, pain, diabetes, obesity, ocular, cardiovascular, or metabolic diseases, should be discussed with the AZ study physician/delegate and documented in the source document. The initiation of new biologic products are not recommended within 12 weeks (≥5 half-lives) after the last dose of IP.
Investigational biologics or non-biologics	**Prohibited**	
Allergen immunotherapy	**Restricted**	It is recommended that patient does not receive allergen immunotherapy on the same day as IP administration.

Table 6 Allowed, restricted, and prohibited concomitant medication

Unless specifically indicated, all conditions apply from enrollment throughout the study duration.
The restrictions below may be waived for patients who have discontinued IP and are in Modified study follow-up (MFU) after Week 56 if the treatment is considered medically necessary by the investigator. Medications not listed in this table are allowed.

Medication	Allowed/Restricted/ Prohibited	Details
Live attenuated vaccines	**Prohibited**	Disallowed within 30 days prior to randomization, during the treatment period and for 12 weeks (≥5 half-lives) after the last dose of IP.
Inhaled marijuana	**Prohibited**	Use of inhaled marijuana is disallowed during the treatment period of the study.

6.5.4.1 COPD medication restrictions on the days of scheduled spirometry visits

Spirometry assessments will be performed at the study site at scheduled visits (see Table 1 and Table 2). There are restrictions regarding the patient's COPD medications prior to the spirometry assessments.

- Run-in period spirometry visits: Patients will be asked to withhold their usual triple (ICS/LABA/LAMA) background medications on the morning of the screening pre- and post-bronchodilator spirometry, preferably for at least 12 hours prior to the assessment (24 hours prior to the assessment for once-daily medications), for the eligibility assessment (see inclusion criterion 5, Section 5.1). In addition, SABA and SAMA should not be used within 6 hours of this spirometry assessment. The patient's usual COPD medications may be administered following completion of the screening lung function procedures. If a patient is unable to meet medication restrictions for spirometry at Visit 1, screening spirometry should be re-scheduled (see Section 4.1.2).
- Treatment period visits with pre-bronchodilator spirometry: Patients will be asked to withhold their usual triple (ICS/LABA/LAMA) background medications on the mornings of the scheduled pre-bronchodilator spirometry visits, preferably for at least 12 hours prior to the spirometry assessment (24 hours prior to the assessment for once-daily medications). In addition, SABA and SAMA should not be used within 6 hours prior to the spirometry assessments. The patient's usual COPD medications may be administered following completion of the pre-bronchodilator spirometry. The IP will be administered at a scheduled visit after the spirometry assessments.

If the patient has taken their usual triple (ICS/LABA/LAMA) background medications on the morning of the scheduled spirometry visit, the investigator/authorized delegate should remind the patient of the importance of withholding their usual morning maintenance therapy and re-schedule the spirometry assessment (and IP dosing) for another day, within the allowed window. If re-scheduling is absolutely not feasible for the patient, spirometry may be performed with a notation indicating that the lung volume measurements and/or spirometry

were performed after the usual triple (ICS/LABA/LAMA) background medications administered.

If the patient has taken the rescue SABA or SAMA within 6 hours of the planned spirometry visit, they should ideally remain at the site until such time that the 6 hours withholding time has been reached or return on another day within the visit window. If neither option is feasible for the patient, spirometry may be performed with a notation indicating that the lung volume measurements and/or spirometry were conducted within 6 hours of SABA/SAMA use.

6.5.4.2 COPD medication restrictions at unscheduled visits

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

6.6 Dose modification

Not applicable.

6.7 Treatment after the end of the study

Not applicable.

7 DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of IP

Discontinuation from IP does NOT automatically lead to a complete withdrawal from the study. Patients discontinuing from IP are strongly encouraged to continue in the study up to the study completion as described in Section 7.1.1.

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse event that, in the opinion of the investigator, contraindicates further dosing.
- Risk to patient as judged by the investigator or AstraZeneca.
- Severe non-compliance with the Clinical Study Protocol.
- Eligibility requirement found not to be fulfilled that in the opinion of the investigator or AstraZeneca may put the patient at risk.
  If a patient does not meet all the eligibility criteria but is randomized in error, the investigator should inform the AZ study physician immediately to discuss potential safety concerns and the best interests of the patient, and decide on further patient's disposition.

- Pregnancy.
- Lost to follow up.
- Development of any study-specific criteria for discontinuation:
  - Anaphylactic reaction to the IP requiring administration of epinephrine
  - Development of helminth parasitic infestations requiring hospitalization
  - Intensive care unit admission with prolonged intubation and mechanical ventilation for a COPD-related event

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

Before a decision to discontinue a patient from IP is instituted, the investigator should carefully consider whether continuation on IP or discontinuation of IP will be in the best interest of the patient and whether the issue can be mitigated by postponing or skipping the dose. It is highly recommended that the AZ study physician be consulted before the IP discontinuation transaction takes place. In case of safety concerns IP administration may be immediately withheld until the final decision is made.

The reason for premature discontinuation of IP should be documented in source documentation and recorded in the eCRF. Conditions that require administration of IP to be temporarily withheld are described in Section 6.1.1.

7.1.1 Procedures for discontinuation of IP

The investigator should contact the patient if a decision to stop IP is taken. A patient who decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. The date of last IP dose, the date of IP discontinuation decision, and the reason(s) for discontinuation should be documented in source documentation and recorded in the eCRF.

Discontinuation of IP will be registered in the IWRS.

Patients who prematurely discontinue IP should return to the study site and complete the IPD visit procedures. It is recommended that the IPD visit is performed within 8 to 12 weeks after the last dose of IP (see Table 1 and Table 2) or as soon as feasible after a decision on IP discontinuation has been taken. It is strongly recommended that all scheduled study visits and procedures are continued until the IPD visit, if possible; if the patient is unable to attend a scheduled clinic visit they should be contacted via phone to collect information pertaining to the respective visit.

The patient must bring the eDiary to the IPD visit for the forced data transfer.

At the IPD visit, the patient will be offered the following options for further follow-up:

Before Week 56

- Clinic+Phone follow-up (FU): Patients who discontinue IP before Week 56 are encouraged to return for all regular clinic and phone call visits until they complete a total of 56 weeks in the study. No PK, ADA, or biomarker samples will be collected after the IPD visit for discontinued patients.
- Phone FU only: If the patient cannot comply with the option above, he/she will be offered a Phone FU option that includes monthly phone calls and continued eDiary completion, until the patient completes 56 weeks in the study. The key elements to be collected at Phone FU visits are listed in Table 1.

After Week 56

- Modified study follow-up (MFU): All patients who discontinue IP at or after Week 56 and patients who reach Week 56 that are in FU already will continue the study in MFU beyond Week 56 until study completion.
  - The patients will be contacted every 4 weeks to collect key information listed in Table 2 until study completion.
  - The patient may choose phone only contacts or site visits every 8 weeks and phone contacts in between (as per original schedule). The patient may switch between the options upon agreement with the study site.
  - The investigator may request that particular MFU visits are performed on-site or perform unscheduled visit(s) (e.g. if needed to evaluate potential COPD symptoms worsening). Additional assessments performed at these visits are at the discretion of the investigator.
  - MFU option may also include contact with a relative or treating physician and collection of information from medical records.
  - Patients entering MFU will return their eDiary at Week 56 or IPD visit, as applicable.
  - Patients in MFU will not have an EOT visit.

The decision on selected follow-up option(s) needs to be documented. A patient who agrees to Phone FU or MFU option is not considered to have withdrawn consent or to have withdrawn from the study.

All patients discontinued from IP will continue in the study follow-up until the study is completed.

AstraZeneca will continue to provide/reimburse allowed background COPD medications up to study completion or withdrawal.

The investigator will be instructed to force data transfer from the eDiary on the day of IPD visit and then to re-dispense the device to patient for continued completion up to Week 56. eDiary alerts will still be in place to notify both the patient and the study site of a potential symptom worsening event (see Section 8.1.3.4). The patient will be asked to return the eDiary to the study site at Week 56 or at IPD visit if they discontinue after Week 56.

7.1.2 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be randomized or receive IP. There can be no exceptions to this rule. Patients who are enrolled but subsequently found not to meet all the eligibility criteria must be screen failed using an IWRS.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on IP, the investigator should inform the AZ study physician immediately, and a discussion should occur between the AZ study physician and the investigator regarding whether to continue or discontinue the patient from treatment. The decision should be appropriately documented.

7.2 Lost to follow up

A patient will be considered potentially lost to follow up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

To prevent patients being lost to follow up, their contact details, including next of kin or other emergency contacts, should be collected initially and updated regularly by the site staff or representative (if allowed by national regulation). The investigator should educate the patient on the importance of contact with the investigator throughout the study.

The following actions must be taken if a patient is identified as a potential lost to follow up:

- The site must make an effort to contact the patient to re-schedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Repeated attempts must be made to contact the patient or next of kin/emergency contact via telephone, fax, email, certified letter and/or through patient locator agencies (if allowed by national regulation).
- Repeated attempts must be made to locate and obtain pertinent medical information for the patient via available hospital records, patient's primary physician, and a publicly available death registry to obtain a current survival status (if allowed by national regulation).
- Where permissible by local law, the ICF will include language to grant the option to employ outside companies to assist in obtaining updated contact information or ascertainment of vital status of lost patients using publicly available source.

Efforts to reach the patient should continue until the end of the study.

A patient will be classified as lost to follow up only if he/she has failed to return for the required study visits and his/her vital status remains unknown at the end of the study despite all above listed efforts.

7.3 Withdrawal from the study

A patient may withdraw from the study (e.g. withdraw consent) at any time (IP **and** assessments), at his/her own request, without prejudice to further treatment.

A patient who considers withdrawing from the study must be informed by the investigator about available follow-up options (e.g. telephone contact, a contact with a relative or treating physician, or information from medical records) and encouraged to attend an IPD visit within recommended 8 to 12 weeks after the last dose of IP. If the patient agrees to the IPD visit and/or follow-up contact(s) or data collection, the date of consent withdrawal is considered to be the date of the last study-related contact/data collection to which the patient agreed. All the details on the patient's decision must be clearly documented.

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The investigator will follow up with a patient as medically indicated. AstraZeneca or its delegate will request investigators to collect information on patients' vital status (dead or alive; date of death when applicable) at the end of the study from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study end in all patients is crucial for the integrity of the study.

The patient should return all IP, eDiary, and unused background/rescue medications provided by the sponsor.

It is the investigator's responsibility to fully evaluate the patient upon discontinuation or withdrawal to ensure that the patient receives appropriate treatment according to his/her clinical status/condition.

7.3.1 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. The collection of the biological samples is

an integral part of the study where mandatory sampling conform with the clinical safety laboratory test requirements.

- A patient who does not allow for further collection or analysis of the mandatory biologic samples critical for clinical safety laboratory tests will need to be discontinued from IP.
- In the case where a patient allows for collection and analysis of biological samples but specifically withdraws his/her consent for the use of voluntary samples for exploratory research (see Table 3) or the retention of samples for exploratory research after the end of the study, the patient does not need to be discontinued from IP and will be allowed to continue participation in the study.

Additional actions to be taken in the event of withdrawal of consent for donated biological samples are described in Appendix C 2.

7.3.2 Withdrawal due to recruitment completion in a randomization stratum

When a cohort of 2 exacerbations in the previous year is full, patients qualifying for the completed cohort will not be randomized and will be withdrawn from the study (screen failed) using an IWRS. The reason for study withdrawal should be documented in the source and eCRF as 'development of study-specific criteria for discontinuation'. No further study related follow up of these patients is required.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1 and Table 2).

The investigator will ensure that data are recorded on the eCRF. The Web-based data capture (WBDC) system will be used for data collection and query handling.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue IP.

Adherence to the study design requirements, including those specified in the SoA (Table 1 and Table 2), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of

all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Table 1).

8.1 Efficacy assessments

8.1.1 Assessment of COPD exacerbations

For the purpose of the protocol, 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

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 due to COPD.

An eDiary alert system will be in place to notify both the patient and the study site of a potential symptom worsening that warrants a contact between the patient and the site for further evaluation. See Section 8.1.3.4 for details.

Patients will be encouraged to contact the study site and/or their primary care physician in case of COPD symptoms worsening even if an eDiary alert is not triggered. The patients will be asked to inform the investigator of any COPD-related events treated outside of the study site.

If an exacerbation event is not associated with an eDiary symptom worsening alert (e.g. technical issue, patient self-reports symptom worsening/exacerbation event, the exacerbation is identified during a visit or phone contact, exacerbation is evaluated and treated at non-study site, or an acute/severe symptom deterioration that is not captured in the eDiary system), the

investigator should interview the patient and evaluate potential worsening and duration of the following symptoms:

- Dyspnea
- Sputum volume
- Sputum purulence
- Cough
- Wheezing
- Other COPD- related symptoms and/or findings (e.g. chest tightness, fatigue etc.)

The investigator should record all pertinent findings and symptoms associated with the exacerbation event and their duration in source documents and in the eCRF COPD exacerbation module.

A vast majority of COPD exacerbations are associated with worsening of the symptoms described above. Clinical presentations may, however, vary among patients. If it is not possible to capture the symptoms as described above (e.g., patient intubated upon arrival to the emergency department), the investigator must document the justification for defining the event as an exacerbation and record it in the eCRF. Death due to COPD will always be captured as severe COPD exacerbation irrespectively of associated symptom worsening.It is recommended that medications to treat a COPD exacerbation are not used for more than 14 days. Recent data suggest that treatment with systemic corticosteroids for shorter periods of time results in similar outcomes with less systemic steroid exposure (Leuppi et al 2013). During a COPD exacerbation, it is important for subjects to be treated as deemed appropriate by the treating healthcare provider. However, all supplemental medication used to treat the COPD exacerbation should be discontinued as soon as it is considered safe by the investigator and subjects should return to their pre-exacerbation medication regimen as soon as practical.

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.

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

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

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

8.1.2 Spirometry (pre- and post-bronchodilator assessments at clinic visits)

General requirements

Lung function (FEV_1 and FVC) at the study site will be measured by spirometry using equipment provided by a central vendor. The central spirometry vendor is responsible for assuring that the spirometer meets American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations and that the study site personnel who will be performing the testing are properly certified.

Spirometry will be performed by the investigator or authorized delegate according to ATS/ERS guidelines (Miller et al 2005).

Spirometry calibration and data quality checks (including monitoring of unexpectedly high variability of results) will be detailed in a separate spirometry procedures manual. Patients who exhibit unexpectedly high variability of FEV_1 will be evaluated by the investigator for etiology of variability, necessary follow-up actions, and assessment of continued patient eligibility. The investigator will discuss unexpectedly high variability with the AZ study physician (see Section 4.1.2).

Important! Patients should be instructed not to use their ICS/LABA/LAMA medication within 12 hours (24 hours for once daily medications) of scheduled site visit spirometry as this will affect the pre-/post-bronchodilator FEV_1 value; they may be taken subsequently, at the site. For the same reason, patients should not use their rescue (SABA and/or SAMA) medication within 6 hours of a scheduled site visit spirometry.

Options for handling patients who have inadvertently taken their COPD medication within the restricted window are described in Section 6.5.4.1.

Time of day for scheduled site visit spirometry

Spirometry testing should be done according to the schedule provided in Table 1 and Table 2. It is recommended that all post-randomization spirometry assessments are performed within ±1.5 hours of the time of day that the randomization spirometry is performed, if possible.

Spirometry technique

Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements or eating a large meal for at least 2 hours prior to spirometry measurements at the site. Forced expiratory maneuvers should be performed with the patient seated in an upright position. If this is not comfortable for the patient, standing is permitted.

The same position should be used by the patient for each forced expiratory maneuvers from enrollment throughout the study. The head must not be tilted during maneuvers and the thorax should be able to move freely; hence tight clothing should be loosened. A nose-clip should be used for the maneuver. The patient should use mouthpieces of the same dimension and shape from enrollment throughout the study.

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

Multiple forced expiratory efforts (at least 3, but no more than 8) will be performed for each site spirometry session. Spirometry grading will conform to ATS/ERS acceptability and reproducibility criteria as detailed in the spirometry manual. The highest FEV_1 and FVC will be based on the best efforts meeting acceptability criteria. The highest recorded FEV_1 and FVC do not need to be from the same effort and can be derived from separate efforts. The absolute measurement (for FEV_1 and FVC), and the percentage of predicted normal value (Quanjer et al 2012) will be recorded. Further details on spirometry are provided in the spirometry manual.

Post-bronchodilator spirometry

Post-bronchodilator spirometry will be performed at Visit 1 for all patients (to evaluate inclusion criterion 5, see Section 5.1).

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

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

The patient's usual COPD morning maintenance therapy must not be given until after the initial pre-medication, pre- and post-bronchodilator spirograms are complete for the reasons discussed above. IP dosing should be given after spirometry is complete. If the patient cannot tolerate a spirometry assessment during the visit, it can be re-scheduled for a different date, preferably within the visit window. There is no need to withhold IP in this case, it can be administered during the visit as scheduled.

Record keeping

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

Spirometry references

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

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

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

8.1.3 Patient-reported Outcomes

Patients will complete all Patient Reported Outcome (PRO) assessments using an electronic handheld device (i.e. eDiary) during the run-in and treatment period. PRO assessments must be collected in a systematic way to ensure data integrity. Best practice guidelines should be followed when collecting PRO data; these guidelines are described in Appendix E. Compliance with eDiary completion must be checked at each study visit and should be checked more frequently to identify problems early (see Appendix E).

The following PRO assessments will be completed, as per Table 1 and Table 2:

- Daily: EXACT-PRO/E-RS:COPD (first 56 weeks only), background medication use, rescue medication use, and symptom severity questionnaire
- Every 4 weeks for the first 56 weeks, and every 24 weeks thereafter: SGRQ, CAT, and EQ-5D-5L
- 1 week after each scheduled visit for IP administration: Onset of Effect Questionnaire (OEQ) – Question 1 (first 56 weeks only)

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

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

exacerbation event. In identifying event onset and recovery, the EXACT-PRO can provide information on event frequency and duration as well as event severity.

The E-RS: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 and 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.

8.1.3.2 Background medication use

Background medication adherence will be assessed daily via a single yes/no question on the eDiary. The patient will be asked if they took their regularly scheduled COPD medicine (yes/no) and instructed not to consider instances of rescue inhaler usage when answering this question.

8.1.3.3 Rescue medication use

Rescue medication usage, including reliever inhaler and nebulizer (e.g. SABA and/or SAMA) use, will be recorded daily on the eDiary. Inhaler usage will be reported as the number of puffs over the last 24 hours, whereas nebulizer use will be reported as the number of times over the last 24 hours.

8.1.3.4 Symptom severity questionnaire and alert system

The severity of COPD symptoms will be assessed daily for the purposes of a symptom worsening alert. The purpose of this alert is to notify both the patient and the study site of a potential symptom worsening that warrants contact between the patient and site for further evaluation.

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

If symptoms meet a specific threshold (i.e. 1 major COPD symptom and at least 1 other major or minor symptom for 2 consecutive days), the eDiary generates an alert to the subject and the investigational site. This alert should trigger a contact between the subject and the investigational site. The Investigator should follow up with the patient as soon as possible to decide on the need for further evaluations and/or treatment.

8.1.3.5 St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item PRO instrument developed to measure the health status of patients with airway obstruction diseases (Jones et al 991). The questionnaire is divided into two parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and 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 2009).

The patient will complete the SGRQ on the eDiary at the site for Visit 1 (screening), Visits 2/2.X (run-in period), and Visit 3 (randomization) prior to other study procedures. During the treatment period up to Week 56, the SGRQ will be available every 28 ±7 days, to be completed preferably at home prior to the study visit or at the site during the scheduled visit. After Week 56, the SGRQ will be available every 168 ±7 days, to be completed preferably at home prior to the study visit or at the site during the scheduled visit.

8.1.3.6 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 adjectives to capture the impact of COPD. Content includes items related to cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep, and energy. A CAT total score is the sum of item responses. Scores range from 0 to 40 with higher scores indicative of greater COPD impact on health status.

The patient will complete the CAT on the eDiary at the site for Visit 1 (screening), Visits 2/2.X (run-in period), and Visit 3 (randomization) prior to other study procedures. During the treatment period up to Week 56, the CAT will be available every 28 ±7 days, to be completed preferably at home prior to the study visit or at the site during the scheduled visit. After Week 56, the CAT will be available every 168 ±7 days, to be completed preferably at home prior to the study visit or at the site during the scheduled visit.

8.1.3.7 European Quality of Life-5 Dimensions (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 analog scale (VAS), 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 patient will complete the EQ-5D-5L on the eDiary at the site for Visit 1 (screening), Visits 2/2.X (run-in period) and Visit 3 (randomization) prior to other study procedures. During the treatment period up to Week 56, the EQ-5D-5L will be available every 28 ±7 days, to be completed preferably at home prior to the study visit or at the site during the scheduled visit. After Week 56, the EQ-5D-5L will be available every 168 ±7 days, to be completed preferably at home prior to the study visit or at the site during the scheduled visit.

8.1.3.8 Onset of Effect Questionnaire

The Onset of Effect Questionnaire (OEQ) is a 5-item assessment of patient-perceived medication effects with a 1-week recall period (Leidy et al 2008). Respondents are to report the degree to which they agree or disagree with 5 statements concerning their perception of and satisfaction with the onset of a study medication. Response options for all questions are: strongly agree, somewhat agree, neither agree nor disagree, somewhat disagree, and strongly disagree.

The patient will complete only OEQ item 1 ("During the past week, you could tell that your study medication was working.") in this study. The OEQ item will be completed on the eDiary 7±2 days after each scheduled visit for IP administration up to Week 48, as indicated in Table 1.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA (Table 1 and Table 2).

8.2.1 Clinical safety laboratory assessments

The clinical chemistry, hematology, and urinalysis will be performed at a central laboratory. All protocol-required laboratory safety tests, as defined in Table 7, must be conducted in accordance with the schedule provided in Table 1 and Table 2 and the procedures described in the laboratory manual.

See Table 7 for the list of clinical laboratory safety tests to be performed.

Screening absolute blood eosinophil count will be assessed at Visit 1 by the central laboratory as part of hematology safety testing.

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The copy of the laboratory result report should be signed and dated by the investigator and retained at the study site as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

Table 7 Laboratory safety variables

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

[a] Eosinophil, basophil, and monocyte counts will be redacted from the central laboratory reports starting from Visit 3 (see Section 6.3.2).

[b] Measured as bicarbonate.

8.2.1.1 Other laboratory assessments

Serology

Blood samples for the hepatitis B surface antigen, hepatitis C antibody, p24 antigen, and the HIV-1 and HIV-2 antibodies will be taken at Visit 1. The analysis will be performed at the central laboratory. Any low-positive or indefinite results must be confirmed prior to determining the patient's eligibility.

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

8.2.2 Pregnancy test

The following tests are applicable to female patients of childbearing potential only and will be conducted as per the schedule provided in Table 1 and Table 2.

- FSH: The test will be performed at Visit 1 only, for female patients, to confirm postmenopausal status in women <50 years of age who have been amenorrheic for ≥12 months.
- Serum beta-human chorionic gonadotropin (HCG): The test will be performed at Visit 1 only, for WOCBP (analyzed at the central laboratory).
- Urine HCG: The dipstick test will be performed at the study site for WOCBP as per the schedule provided in Table 1 and Table 2. At each treatment visit, the test will be performed before IP administration. A positive urine test result must be confirmed with a serum beta-HCG prior to administration of IP.
  Patient WOCBP who are doing optional remote visits with IP self-administration (after week 56) will be provided with urine pregnancy dipstick test and advised to perform the test prior to IP self-administration. If the urine pregnancy test result is positive, the patient should contact the site and should not administer IP. A positive urine test result must be confirmed with a serum beta-HCG prior to administration of IP.

8.2.3 Physical examinations

Physical examinations (complete or brief) will be done in accordance with the schedule provided in Table 1 and Table 2. Baseline data will be collected at the randomization visit (Visit 3) before first dose of IP. Any new findings or aggravated existing abnormalities, judged as clinically significant by the investigator, will be reported as an AE as described in Section 8.3.7.

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

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

8.2.3.1 Weight and height

The patient's height will be measured at Visit 1 only. Weight will be measured in accordance with the schedule provided in Table 1 and Table 2. The patient's weight will be recorded in kilograms and height will be recorded in centimeters.

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

8.2.4 Smoking status

Smoking status will be assessed at each visit starting from Visit 1 through EOT by collecting the patient's response to a single yes/no question from study personnel: 'What is your smoking status as of today, do you currently smoke?'

Use of e-cigarettes is discouraged during the study; it should be captured in source documentation and eCRF.

8.2.5 Vital signs

Pre-dose vital signs (pulse rate, blood pressure, respiratory rate, body temperature, and oxygen saturation [SpO_2]) will be assessed in accordance with the schedule provided in Table 1 and Table 2.

It is recommended that vital signs are assessed before any interventional study procedures (blood test collection, spirometry, IP administration), and prior to administration of COPD maintenance therapy, if possible.

Blood pressure and pulse measurements will be assessed while sitting with a completely automated device. Manual techniques will be used only if an automated device is not available. The pulse rate and blood pressure should be measured after the patient has been resting for at least 5 minutes in a quiet setting without distractions (e.g. television, cell phones). The pulse rate will be obtained before blood pressure.

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

Pulse oximetry will be used to measure oxygen saturation.

Body temperature will be measured in Celsius; oral measurement is preferred, but other methods are acceptable as per local standards of care.

8.2.6 ECG

Single 12-lead ECG will be obtained as outlined in the SoA provided in Table 1 and Table 2. ECG will be obtained using an ECG machine provided by a central vendor that automatically calculates the heart rate and measures PR, QRS, and QT intervals; only this equipment should be used for assessment throughout the subject's participation in the study. The ECG results will be transmitted to a central reader.

The investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. The ECG printouts will be signed and dated by the investigator and stored at the study site. Any findings will be recorded in the eCRF.

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

8.3 Collection of adverse events

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

The definitions of an AE or SAE can be found in Appendix B.

An AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow-up AEs, see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

Adverse Events will be collected from randomization (Week 0) throughout the treatment period and including the phone follow-up period. In Modified study Follow-up period (see Section 7.1.1), non-serious adverse events will be captured if they are considered related or led to discontinuation of IP and/or the study.

SAEs will be recorded from the time of signing of ICF throughout the duration of the study.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs in former study patients. However, if the investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to IP or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow up.

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

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

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

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

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

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

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- AE is serious due to (see definition of serious AE in Appendix B 2)
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)

- Causality assessment to other medication

8.3.5 Causality collection

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

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

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

8.3.6 Adverse events based on signs and symptoms

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

8.3.7 Adverse events based on examinations and tests

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

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

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see Section 8.3.8.

8.3.8 Disease-under study (DUS)

Any event attributable to disease under study (COPD) and/or its progression (increase in the symptoms of the disease, e.g. dyspnea, mucus production, cough etc, and/or increase in the severity of the disease) should be considered as disease under study and not an AE, unless it meets the definition of an SAE (see Appendix B).

COPD worsening that meets the protocol definition for COPD exacerbation (Section 8.1.1) will be captured on a specific eCRF module.

COPD exacerbation should not be reported as an AE unless it meets the definition of an SAE (see Appendix B). In such case, COPD exacerbation should be reported both as an exacerbation and as an SAE.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

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

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

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

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

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

If the WBDC system is not available, then the investigator or other study site personnel reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site personnel how to proceed.

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

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

8.4.2 Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.4.3 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study patient has received any IP

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.3.1 Maternal exposure

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

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

If any pregnancy occurs in the course of the study, then the investigator or other study site personnel informs the appropriate AstraZeneca representatives within 1day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.4.4 Overdose

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

There is no specific treatment for an overdose with benralizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within **one calendar day** (fatal/life-threatening SAE) or **5 calendar days** (all other SAEs) for overdoses associated with an SAE (see Section 8.4.1) and **within 30 days** for all other overdoses.

8.4.5 Medical Device Deficiencies

- Medical devices are being provided for use in this study as the study intervention is supplied in prefilled syringes are being utilized to deliver the IMP under study. In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the

detection and documentation of events meeting the definitions of medical device deficiency that occur during the study with such medical devices.

The definition of a Medical Device deficiency can be found in Appendix J.

NOTE: Incidents and deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix J of the protocol.

In this study any deficiency observed with a third-party medical device will be collected and reported to the manufacturer.

A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

The AstraZeneca medical device complaint report will be used to collect the deficiency.

8.4.5.1 Time Period for Detecting Medical Device Deficiencies

Medical device incidents or malfunctions of the medical device will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any medical device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting Medical Device Deficiency is provided in Appendix J.

8.4.5.2 Follow-up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.5.3 Prompt Reporting of Medical Device Deficiencies to Sponsor

Medical device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.

The Medical Device Deficiency Paper Report Form will be sent to the sponsor by e-mail (AEMailboxClinicalTrialTCS@astrazeneca.com). If e-mail is unavailable, then fax (AstraZeneca designated fax +1 302 886 4114) should be utilised.

The sponsor will be the contact for the receipt of medical device deficiency reports.

8.4.5.4 Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all medical device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of medical device deficiencies to the IRB/IEC.

For further guidance on the definition of an SAE, see Appendix J of the CSP.

8.4.6 Medication error, Drug Abuse, and Drug Misuse

8.4.6.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.4.1) and **within 30 days** for all other events.

8.4.6.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant. The full definition and examples of medication error can be found in Appendix B 8.

8.4.6.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect. The full definition and examples of drug abuse can be found in Appendix B 8.

8.4.6.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route. The full definition and examples of drug misuse can be found in Appendix B 8.

8.4.7 Management of IP-related anaphylaxis

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

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

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

Further details on the clinical criteria for defining anaphylaxis and immune complex disease are provided in Appendix F 2.

Patients will have a pre-assessment (i.e. vital signs and lung function) prior to IP administration) and should be observed (or contacted when participating in the self-administration program) after IP administration for the appearance of acute drug reactions in line with the clinical practice.

Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local or central lab at the discretion of the investigator.

8.5 Pharmacokinetics

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

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

Serum will be collected pre-dose in accordance with the schedule provided in Table 1 and Table 2. Samples will be collected, labelled, stored, and shipped as detailed in the laboratory manual.

8.5.1 Determination of drug concentration

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

The following samples will be analysed: PK samples from patients assigned to the benralizumab treatment group (including baseline).

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

8.5.2 Storage and destruction of pharmacokinetic samples

Samples may be stored for a maximum of 5 years from the date of the last patient's last visit, after which they will be destroyed.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Guidance regarding handling, transport, and destruction of human biological samples is provided in Appendix C.

8.6 Pharmacodynamics

Blood eosinophil levels will be assessed as part of the hematology safety testing, see Section 8.2.1. Biomarkers CCI [redacted] CCI [redacted] may also be assessed as part of exploratory research, see Section 8.8.

8.7 Genetics

8.7.1 Optional exploratory CCI sample

A blood sample for CCI will be collected at one time point only from patients who have consented to participate in the CCI analysis component of the study. Participation is optional. Patients who do not wish to participate in the CCI research may still participate in the study.

Samples can be collected at any time after the CCI consent 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 failure, a replacement CCI blood sample may be requested from the patient.

See Appendix D for information regarding CCI research. Details on processes for collection, shipment, and destruction of these samples can be found in Appendix D or in the Laboratory Manual.

8.7.2 Storage and destruction of CCI samples

The processes adopted for the coding and storage of samples for CCI analysis are important to maintain patient confidentiality. Samples may be stored for a maximum of 15 years or as per local regulations from the date of the Last Patient's Last Visit, after which they will be destroyed. CCI is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organizations working with the CCI.

8.8 Biomarkers

CCI for exploratory analysis will be collected prior to IP administration for all patients, in accordance with the schedule provided in Table 1.

Analysis will be performed on biomarkers CCI
CCI
CCI 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. These analyses should provide a better understanding of the effects of benralizumab on biomarkers CCI. Results from the exploratory biomarker analyses will be reported separately from the CSR. (Investigators will not receive the results.)

CCI is the study of the CCI, CCI that are produced by CCI, using CCI methods. These include, but are not limited to CCI and CCI technologies. CCI analysis will be performed on CCI from CCI CCI samples.

Exploratory biomarker samples will not be collected in China.

8.8.1 Storage, re-use, and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the date of the last patient's last visit, after which they will be destroyed.

The results of this biomarker research may be pooled with biomarker data from other studies of benralizumab to provide data for greater understanding of pathophysiology of COPD and possible patient subsets.

Guidance regarding handling, transport, and destruction of human biological samples is provided in Appendix C.

8.9 Immunogenicity assessments

Antibodies to benralizumab will be evaluated in serum samples collected from all patients according to the SoA (Table 1 and Table 2). Additionally, serum samples should also be collected at the final visit from patients who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for anti-benralizumab (drug) antibodies (ADA) and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to benralizumab and/or further characterize the immunogenicity of benralizumab.

The detection and characterization of antibodies to benralizumab will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to benralizumab will also be evaluated for benralizumab serum concentration to enable interpretation of the antibody data.

Samples may be stored for a maximum of 5 years (or according to local regulations) following the last patient's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to benralizumab.

8.10 Healthcare resource utilization and health economics

Broad-based COPD-related healthcare resource utilization information will be collected by the investigator/authorized delegate in accordance with the schedule provided in Table 1 and Table 2 and recorded in the appropriate eCRF module.

At randomization (Week 0), COPD-related healthcare resource utilization information will be collected with a 1-year recall period. All the subsequent visits will collect COPD-related healthcare resource utilization information with a recall period of 'since last scheduled visit'.

Note: cases of hospitalization also must be reported as an SAE (see Section 8.4.1).

8.11 Other assessments and procedures

8.11.1 Supplemental oxygen (O_2)

Oxygen use will be assessed at each clinic visit according to the schedule in Table 1 and Table 2. Use of oxygen should be recorded as a concomitant medication in eCRF.

8.11.2 Chest CT scan/X-ray

CCI [redacted]

CCI the CT scan (or an X-ray) is required to ensure there are no abnormal radiological findings that would exclude the patient from study participation, as per exclusion criterion 3 (see Section 5.2).

If a historical (previously done) CT is available, dated within 6 months prior to enrollment or obtaining informed consent, this may be utilized both for the evaluation of exclusion criterion 3 CCI [redacted]. The images should be assessed at the site (including clinical interpretation by a radiologist or a Physician qualified to read and interpret radiological chest examinations per local standard practice) CCI [redacted]

If a historical CT is not available, a new CT scan should be performed during the run-in period. In order to avoid radiation exposure to screen failed subjects, this should be performed after key inclusion criteria have been confirmed. CCI [redacted]

- CCI [redacted]
- CCI [redacted]

- CCI
- CCI

All new CT scans should be performed post-bronchodilation, i.e. within 60 minutes of using up to 4 inhalations of albuterol or salbutamol.

CCI
CCI
CCI
CCI

If neither historical or screening CT can be obtained (e.g. in case of clinical contraindications, access issues, or patient's refusal), a chest X-ray (with clinical interpretation by a Radiologist or a Physician qualified to read and interpret radiological chest examinations per local standard practice) performed within 6 months prior to enrollment or during the run-in period must be obtained to inform exclusion criterion 3 prior to randomization. CCI
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Any clinical findings from historical CT or chest X-ray should be recorded on the specific imaging eCRF page for Visit 1. Any findings based on the local assessment of a new CT scan (or X-ray) performed during screening/run-in must be recorded in the corresponding eCRF section for Visit 2.

CCI

8.11.3 Pneumococcal and annual influenza vaccination

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

the vaccination should be given at the next autumn or winter period. If a patient has an egg intolerance or refuses to be vaccinated, the vaccination may be omitted. If the investigator makes a decision to not vaccinate with either vaccine, the rationale should be clearly specified.

Pneumococcal and/or annual influenza vaccination can be given at Visit 1 or at any other visit throughout the study (except for ±7 days of IP administration) at the discretion of investigator.

8.11.4 Patient Testing Due to Public Health Crisis

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

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

The primary efficacy endpoint is the annualized rate of moderate and severe COPD exacerbations over the first 56 weeks. The primary endpoint will be assessed first in the primary population (patients with ≥3 exacerbations in the previous year) and then assessed on the overall population of patients with ≥2 exacerbations in the previous year. A treatment policy estimand will be applied to the primary analysis of the primary endpoint whereby all data is included, regardless of whether a patient remains on blinded IP or not.

The null hypothesis is that the exacerbation rate on benralizumab 100 mg is equal to the exacerbation rate on placebo. The alternative hypothesis is that the exacerbation rate on benralizumab 100 mg is not equal to the exacerbation rate on placebo, i.e.:

H_0: Rate ratio (benralizumab 100 mg vs. Placebo) = 1

H_1: Rate ratio (benralizumab 100 mg vs. Placebo) ≠ 1

Hypothesis testing for the primary analysis, annualized rate of moderate and severe COPD exacerbations over 56 weeks in patients with ≥3 exacerbations in the previous year, will be performed at the 2-sided 5% significance level. If the p-value is less than 0.05 and the treatment effect favors benralizumab, reject H_0 and accept H_1.

A multiple testing procedure will be applied to the primary endpoint in the overall population and key secondary endpoints in both the primary and overall populations; details are provided in Section 9.4.4.

9.2 Sample size determination

The study will recruit patients on triple (ICS/LABA/LAMA) background therapy with screening 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 95% power to detect a 30% reduction in benralizumab 100 mg versus placebo. This calculation assumes a 2-sided 5% alpha level, an annual 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, mean follow-up of 2, and a placebo rate ranging from 0.12 to 0.24, power to detect a 40% reduction in the severe exacerbation rate for benralizumab compared to placebo ranges from 63% to 80%.

9.2.1 Blinded sample size reassessment

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 assignment (e.g. post-randomization eosinophil levels). If conducted, this analysis will not lead to any alteration of sample size and therefore will not have any impact on any of the endpoints including the primary endpoint 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.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
All patients analysis set	All patients screened for the study and will be used for reporting of disposition and screening failures

Population	Description
Full analysis set (FAS)	All patients randomized and receiving at least 1 dose of IP, irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the ITT principle. Patients who withdraw consent or assent to participate in the study will be included up to the date of their study termination.
Safety analysis set	All patients who have received at least 1 dose of IP. Erroneously treated patients (e.g. those randomized 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 on one or several occasions received active IP is classified as active. All safety summaries and ADA data will be based on this analysis set.
Pharmacokinetic analysis set	All patients who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations (e.g. disallowed medication) and who had at least 1 quantifiable serum PK observation post first dose. All PK summaries will be based on this analysis set.

EOT end of treatment (visit); FAS Full analysis set; ITT Intent-to-Treat.

9.4 Statistical analyses

All personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol deviations identified.

Analyses will be performed by AstraZeneca or its representatives. A comprehensive Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

9.4.1 Efficacy analyses

9.4.1.1 General principles

Efficacy analyses will be performed using the FAS which will include all patients randomized who receive at least 1 dose of IP, irrespective of their protocol adherence and continued participation in the study, according to the ITT principle. Patients will be analyzed according to their randomized treatment.

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

for the primary endpoint, SGRQ, and FEV_1 and through EOT for severe exacerbations) is included, regardless of whether a patient remains on blinded IP or not.

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

All efficacy endpoints (listed in Table 8) will be analyzed in patients with a history of ≥3 exacerbations in the previous year (primary population) and repeated in patients with a history of ≥2 exacerbations in the previous year (overall population). 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.

Table 8 Efficacy endpoints

Category	Endpoint	Main timepoint for analysis
Primary	Annualized rate of moderate and severe COPD exacerbations	Over first 56 weeks
Key secondary	Annualized rate of severe COPD exacerbations	Through EOT
	Change from baseline in SGRQ total score	Week 56
	Change from baseline in pre-dose/pre-bronchodilator FEV_1	Week 56
Secondary	Annualized rate of COPD exacerbations that are associated with an emergency room visit or a hospitalization	Through EOT
	Time to the first COPD exacerbation	During first 56 weeks
	Change from baseline in SGRQ domain scores	Week 56
	Change from baseline in CAT total score	Week 56
	Change from baseline in E-RS:COPD total and domain scores	Week 56
	All cause and respiratory-related mortality rate	Through EOT
	Annual rate of hospitalizations due to COPD; Length of hospital stay; ICU days; annual rate of hospitalizations and emergency department visits combined due to COPD; annual rate of unscheduled outpatient visits including unscheduled visits to study sites due to COPD; and annual rate of unscheduled healthcare encounters due to COPD	Through EOT

In situations where additional supportive analyses will be conducted, these will be outlined in the SAP.

CAT COPD assessment tool; EOT End of treatment (visit); E-RS:COPD Evaluating Respiratory Symptoms in COPD; ICU intensive care unit; SGRQ St. George's Respiratory Questionnaire.

9.4.1.2 Primary analysis method

The primary efficacy variable is the annualized rate of moderate and severe COPD exacerbations over the first 56 weeks, and the primary analysis is to compare the annualized

COPD exacerbation rate of benralizumab 100 mg with placebo in patients with a history of ≥3 exacerbations in the previous year. Hypothesis testing on the primary efficacy variable is described in Section 9.1.

Exacerbation rate in the benralizumab treatment group will be compared to exacerbation rate in the placebo group using a negative binomial model. The response variable in the model will be the number of COPD exacerbations over the first 56 weeks of the treatment period. The model will include covariates of treatment group, region, and the number of exacerbations in the previous year. The logarithm of the follow-up time during the first 56 weeks will be used as an offset variable in the model.

The estimated treatment effect (i.e. the rate ratio of benralizumab versus placebo), corresponding 95% confidence interval (CI), and 2-sided p-value for the rate ratio will be presented. In addition, the exacerbation rate and the corresponding 95% CI within each treatment group will be presented.

Any COPD exacerbation that occurs within 7 days of the last dose of systemic corticosteroids (oral, IM, IV) or antibiotics or the last day of hospitalization for a prior COPD exacerbation will be combined and counted as a single exacerbation event and as the maximum severity between the individual events. Further details on combining exacerbation events will be provided in the SAP. Consistent criteria will be applied to all exacerbation endpoints.

9.4.1.3 Analysis methods for secondary efficacy variables

The primary analysis will be repeated in patients with a history of ≥2 exacerbations in the previous year. All secondary efficacy endpoints will be analyzed in patients with a history of ≥3 exacerbations in the previous year and repeated in patients with a history of ≥2 exacerbations in the previous year. 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.

Annualized rate of COPD exacerbations leading to hospitalization or death (i.e. severe exacerbations) will be analyzed through EOT using a similar negative binomial model as outlined for the primary efficacy variable in Section 9.4.1.2. The annualized rate of COPD exacerbations associated with an emergency room visit or a hospitalization through EOT will be analyzed similarly.

The proportion of patients with ≥1 COPD exacerbation 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.

Time to first COPD exacerbation will be analyzed as another supportive efficacy variable to the primary objective to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment, region, and number of exacerbations in the previous year.

Change from baseline in SGRQ total score and three domain scores (symptoms, activity, and impacts) at Week 56 will be compared between benralizumab and placebo using a mixed-effect model for repeated measures (MMRM) analysis in the FAS. The dependent variable will be the change from baseline in SGRQ score at post-baseline protocol-specified visits (up to the Week 56 visit). 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. The model is:

*Change in SGRQ score = Treatment group + baseline SGRQ score + region + visit + treatment*visit*

The proportion of patients 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 test controlling for region.

Change from baseline in pre-dose/pre-bronchodilator FEV_1 at Week 56 will be analyzed in patients with a baseline pre-dose/pre-bronchodilator FEV_1 and at least one post-randomization pre-dose/pre-bronchodilator FEV_1 using a similar MMRM analysis as the analysis for change from baseline in SGRQ score.

Change from baseline in CAT total score at Week 56 and E-RS:COPD total score and domain scores at Week 56 will be analyzed separately using a similar model to the model for change from baseline in SGRQ score. The proportion of patients with ≥2-point decrease (improvement) in CAT score at Week 56 in the benralizumab group will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for region. The same responder analysis used for CAT will be applied for E-RS:COPD total score with the responder threshold defined as a ≥2-point decrease at Week 56.

The number and percentage of patients who die from any cause, along with the exposure-adjusted mortality rate will be presented by treatment group. Similar presentations will be produced for respiratory-related deaths. If there are sufficient numbers of events, a Cox proportional hazards model may be used to compare time to event for these mortality endpoints between treatment groups.

Annual rates of hospitalizations, hospitalizations and emergency room visits combined, unscheduled outpatient visits including unscheduled visits to study sites, as well as all unscheduled healthcare encounters due to COPD (hospitalizations, emergency room visits, and unscheduled outpatient visits including unscheduled visits to study sites) will be summarized by treatment group.

9.4.1.4 Sensitivity analysis

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

9.4.1.5 Subgroup analysis

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

9.4.2 Safety analyses

All safety analyses will be performed using the safety analysis set.

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) that will have been released for execution at AZ/designee.

Safety data will be presented using descriptive statistics unless otherwise specified.

AEs will be presented for each treatment group by system organ class (SOC) and preferred term (PT) covering number and percentage of patients reporting at least one event and number of events where appropriate.

An overview of AEs will present for each treatment group the number and percentage of patients with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP.

Separate AE tables will be provided taken into consideration relationship as assessed by the investigator, intensity, seriousness, death, and events leading to discontinuation of IP.

An additional table will present number and percentage of patients with most common AEs (frequency of >3%).

In accordance with the requirements of the FDA, a separate table will present non-serious AEs occurring in more than 5% of patients in any treatment group.

Key patient information will be presented for patients with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP.

An AE listing for the safety analysis set will cover details for each individual AE.

Full details of AE analyses will be provided in the SAP.

Treatment emergent

The following events are considered treatment emergent:

- Adverse events with an onset date on or after first dose of IP
- Worsening of pre-existing events on or after first dose of IP

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

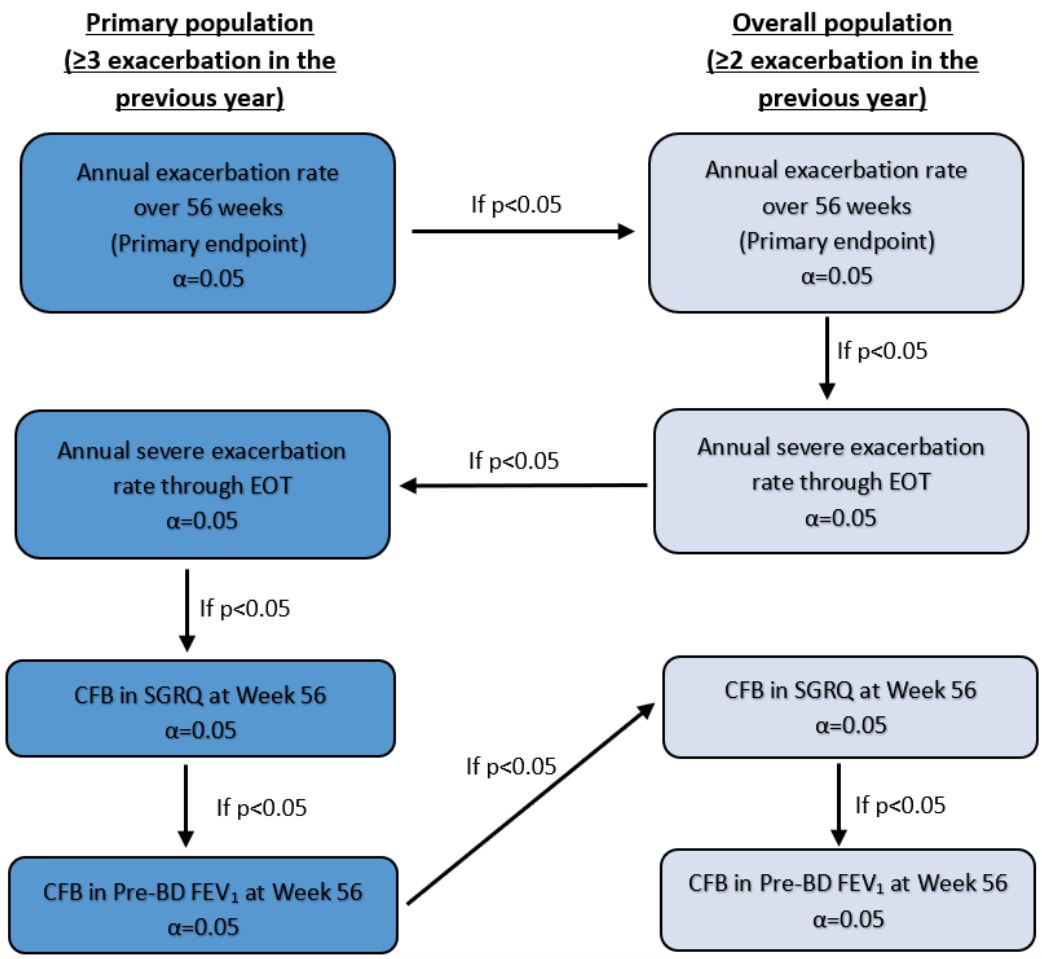
9.4.3 Other analyses

PK, pharmacodynamic, and biomarker exploratory analyses will be described in a separate analysis plan finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the CSR.

9.4.4 Methods for multiplicity control

To account for multiplicity testing for the primary endpoint (annualized rate of moderate to severe COPD exacerbations) and 3 key secondary endpoints (severe exacerbations, change from baseline in SGRQ total score, and change from baseline in pre-dose/pre-bronchodilator FEV_1) in both the primary population (≥3 exacerbations in the previous year) and the overall population (≥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 4.

Figure 4 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 favors the benralizumab treatment arm.

If the null hypothesis for the primary endpoint in the primary population (see Section 9.1) is rejected, with a treatment effect in favor 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 4. 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.

9.4.5 Interim analyses

No interim analysis is planned for this study.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

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

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to the sponsor of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, the sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - The sponsor will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators. If EU Clinical Trials Regulation 536/2014 applies, the sponsor is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
  - the site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - a (potential) serious breach is promptly reported to the sponsor or delegated party, through the contacts (e-mail address or telephone number) provided by the sponsor

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary for the entire study. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date and time the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient.

If a patient declines to participate in any voluntary exploratory research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

Patients who are re-screened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining voluntary samples for future exploratory research to better understand COPD pathogenesis. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analyzed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data Protection

Each patient will be assigned a unique identifier by the sponsor. Any patient records or data sets transferred to the sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov, as will the summary of the study results when they are available. The clinical study and/or summary of the study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 6 Data Quality Assurance

All participant data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Quality tolerance limits (QTLs) will be predefined in the Risk Plan or equivalent to identify systematic issues that can impact participant safety and/or reliability of study result

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan(s).

AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Medical Monitoring Plan(s).

AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.

AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).

Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the

written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 7 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data can be found in the data monitoring plan.

A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first indicator of recruitment is the date when the first study site opens. This date will be the study start date.

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

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

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

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

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

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

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

A 9 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Event Definitions and Additional Safety Information

B 1 Definition of Adverse Events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no IP has been administered.

B 2 Definitions of Serious Adverse Event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above

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

B 3 Life Threatening

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

B 4 Hospitalization

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

B 5 Important Medical Event or Medical Treatment

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

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

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

B 6 Intensity Rating Scale:

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

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe

intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When making an assessment of causality, consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug:

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

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

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

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

B 8 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

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

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

Medication error includes situations where an error:

- Occurred
- Was identified and participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

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

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

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

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody of Biological Samples

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

The investigator at each study site keeps full traceability of collected biological samples from the patients while in storage at the site until shipment or disposal (where appropriate).

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

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

As collection of the biological sample(s) is an integral part of the study where mandatory sampling conforms with the clinical safety laboratory test requirements, then the patient is withdrawn from IP. In the case where a patient allows for collection and analysis of biological samples (for clinical safety laboratory tests) but specifically withdraws his/her consent for the use of voluntary samples for exploratory research or retention of samples for exploratory research after the end of the study, the patient does not need to be discontinued from IP and will be allowed to continue participation in the study.

The investigator or designee:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient
- temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are patient to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk

of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Genetics

D 1 Use/Analysis of DNA

Genetic variation may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well-described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the patient´s DNA, i.e. the entire genome.

The results of genetic analyses may be reported in the Clinical Study Report (CSR) or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on benralizumab continues, but no longer than 15 years or other period, as per local requirements.

D 2 Genetic Research Plan and Procedures

Selection of genetic research population

Study selection record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, patients must fulfill all of the inclusion criteria described in the main body of the Clinical Study Protocol and provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection

Withdrawal of consent for genetic research:

Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.3 of the main Clinical Study Protocol and Appendix C 2.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at randomization (Week 0). Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE); such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Week 0, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample

and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).

The link between the patient enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must give separate consent for this that will be indicated on the main ICF; there is not a separate ICF for genetic sample collection. The investigator is responsible for ensuring that consent is given freely and that the patient understands that they may freely withdrawal from the genetic aspect of the study at any time.

Patient data protection

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

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

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual patient data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

Appendix E Best Practice Guidelines for Completing PRO Assessments

Patients will complete PRO assessments at home using a handheld electronic device (i.e. eDiary). PRO assessments must be collected in a systematic way to ensure data integrity. The following best practice guidelines should be followed when collecting PRO data via an eDiary device:

- Provide the right environment
  - Patients should complete the PRO questions in a quiet and private location without help from others.
- Purpose of the PRO assessments
  - Discuss the purpose of the PRO assessments with the patients. Reinforce that these are standardized questions designed to capture the patient experience in the study.
  - Inform patients that each PRO assessment is independent of the others. Some questions may be very similar or seem repeated, but it is important to answer each question independently.
- Help with procedural questions
  - Make sure the patient understands how to complete the PRO assessment. Assessment instructions are usually self-explanatory, but staff may answer questions about procedural issues like what it means to “tick a box”.
- Avoid bias: do not clarify the meaning of questions or responses
  - Sometimes patients will ask site staff to clarify the meaning of a question or response. To avoid introducing any bias, politely tell the patient that you cannot clarify items. Remind them that there are no right or wrong answers. Inform the patient that they should select the response that best answers the question as they understand it.
  - If a patient becomes unable to independently use eDiary during the treatment period of the study (e.g. unable to read due to vision problems), then the patient should be exempted from completing PRO questionnaires used for efficacy endpoints (EXACT-PRO/E-RS:COPD, SGRQ, CAT, EQ-5D-5L, OEQ) and may continue in the study with external help for symptom severity and background/rescue medication use questionnaires completion. Patient’s exemption in this regard must be pre-approved by AZ study physician/delegate and appropriately documented.
- No time limits
  - Although most PRO assessments require only a few minutes to complete, the patient should be given as much time as is needed.
- Train the patient on eDiary device usage
  - Train patients on how to use the eDiary device using the materials and training provided by the eDiary vendor.

  - Provide guidance on whom the patient should call if they have problems with the device.

- Monitor compliance
  - Minimizing missing data is a key aspect of study success. Compliance with eDiary completion must be checked at each study visit and should be checked more frequently to identify problems early. If compliance with eDiary completion drops below 70% a check-in call from the study site to ask the patient if they are having difficulties is highly recommended.
  - Recommended background medication compliance during the study is ≥70%. It is recommended that compliance levels below 70% prompt the site/investigator to evaluate the reasons for low compliance and to provide re-education to the patient in regards to the importance of compliance. It is strongly recommended that when compliance level falls below 50% the site contacts the AZ study physician in order to discuss reasons for poor compliance and potential impacts on patient's participation in the study.

Appendix F Anaphylaxis: Definition, Signs, Symptoms and Management

F 1 Introduction

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

If an anaphylactic reaction occurs, a blood sample for serum tryptase should be collected at 90 minutes ± 30 minutes after the event; analysis for serum tryptase will be performed at a local or central laboratory. Other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at the discretion of the investigator.

F 2 Clinical Criteria for Defining Anaphylaxis and Immune Complex Disease

Anaphylaxis

In adults, anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

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

   AND AT LEAST 1 OF THE FOLLOWING:

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

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

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

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

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

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

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

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

Immune Complex Disease

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

F 3 Signs and Symptoms and Management of Acute Anaphylaxis

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

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

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles
- Rhinorrhea
- Change in voice
- Metallic taste
- Nausea, vomiting, diarrhea, abdominal cramps and bloating
- Lightheadedness
- Headache
- Uterine cramps
- Generalized warmth

F 4 Management of Acute Anaphylaxis

F 4.1 Immediate intervention

1 Assessment of airway, breathing, circulation, and adequacy of mentation.

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

F 4.2 Possibly appropriate, subsequent measures depending on response to epinephrine

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

(b) Establish and maintain airway.

(c) Administer oxygen.

(d) Establish venous access.

(e) Normal saline IV for fluid replacement.

F 4.3 Specific measures to consider after epinephrine injections, where appropriate

(f) Consider epinephrine infusion.

(g) Consider H1 and H2 antihistamines.

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

(i) Consider systemic corticosteroids.

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

(k) Consider glucagon for patient taking β-blocker.

(l) Consider atropine for symptomatic bradycardia.

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

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

Adapted from Kemp et al 2008.

Appendix G Inhaled Corticosteroids Dose Conversion

ICS component	Conversion factor (i.e. multiply dose by X)	Minimum acceptable daily dose (mcg)
Fluticasone propionate	1	250
Fluticasone propionate HFA (Flovent HFA)	1.14	220 (per actuation)
Fluticasone furoate	2.5	100 (metered)/ 92 (delivered dose)
Budesonide	0.63/ 0.78	400 (metered) / 320 (delivered dose)
Budesonide (nebulized)	0.5	0.5mg (1 ml)
Beclomethasone	0.5	500
Beclomethasone (Trimbow)	1.25	200 (metered)/ 174 (delivered dose)
Beclomethasone extra-fine particles and HFA (Fostair, QVAR)	1.04/ 1.25	250 (metered)/ 200 (per actuation)
Ciclesonide	1.56	160
Mometasone	1.14	220 (metered) 200 (per actuation)
Flunisolide	0.25	1000
Triamcinolone	0.25	1000

Sources: GOLD 2019; GINA 2019

Example conversion

Converting budesonide (delivered dose) to fluticasone propionate (in mcg):

For a budesonide dose of 160 mcg, use a conversion factor of 0.78

160 mcg of budesonide x 0.78 = 124.8 mcg fluticasone propionate equivalent

Appendix H Abbreviations

Abbreviation or special term	Explanation
ADA	Anti-drug antibodies
AE	Adverse event
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
ALT	Alanine aminotransferase
APFS	accessorized prefilled syringe
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BSSR	Blinded sample size re-estimation
CAT	COPD assessment tool
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EOT	End of treatment
EQ-5D-5L	European Quality of Life-5 Dimensions
ERS	European Respiratory Society
E-RS:COPD	Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease
EU CTR	European Union Clinical Trials Regulation
EXACT-PRO	Exacerbations of Chronic Pulmonary Disease Tool – Patient-reported Outcome
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FU	Follow-up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GRAD	AstraZeneca Global Retention and Disposal

Abbreviation or special term	Explanation
HCG	Human chorionic gonadotropin
HCP	Healthcare provider
HIV-1/2	Human immunodeficiency virus-1/2
ICF	Informed consent form
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL-5	Interleukin-5
IL-5Rα	Interleukin-5 receptor alpha subunit
IP	Investigational product
IPD	Investigational product discontinuation (visit)
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LABA	Long-acting β_2 agonist
LAMA	Long-acting muscarinic antagonist
LH	Luteinizing hormone
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MFU	Modified study follow-up
NIPPV	Non-invasive positive pressure ventilation
OCS	Oral corticosteroid(s)
OEQ	Onset of Effect Questionnaire
PK	Pharmacokinetic(s)
PN	Predicted normal
PPD	Purified protein derivative
PRO	Patient-reported Outcome
PT	Preferred term
QTL	Quality Tolerance Limits
Q8W	Every 8 weeks
CCI	CCI
SABA	Short-acting β2 agonist
SADE	Serious adverse device effect

Abbreviation or special term	Explanation
SAE	Serious adverse event
SAMA	Short-acting muscarinic antagonists
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SoA	Schedule of activities
SOC	System organ class
SpO_2	oxygen saturation
TB	Tuberculosis
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell
WBDC	Web-based data capture
WOCBP	Women of childbearing potential

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

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

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

I 1 Consent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Consent should be obtained for the alternative means of carrying out visits and assessments prior to performing the procedures described in Sections I 2to 8.11. Local and regional regulations and/or guidelines regarding consent of study patients should be checked and followed. Consent may be verbal if allowed by local and regional guidelines (note, in the case of verbal consent the ICF should be signed at the patient's next visit with the study site). Visiting the study sites for the sole purpose of obtaining consent should be avoided.

I 2 Rescreening of Patients To Reconfirm Study Eligibility

In the RESOLUTE study, patients are allowed to re-screen once without the need for additional approval from the AstraZeneca study physician if the patient didn't meet one of the inclusion criteria 4 – 15 unless there was a significant protocol issue during the run-in/screening period during the first enrolment. Ex: significant non-compliance with study procedures, among others.

Patients who screen fail due to exclusion criteria 16-32 and other cases will be considered extraordinary and need discussion/approval case by case with the AstraZeneca study physician.
Patients screen failed due to study disruption can be rescreened. The investigator should confirm this with the designated study physician.

In case when a patient was screen failed due to study disruption, at re-screening their spirometry data from previous screening (including post-BD spirometry and follow up for FEV_1 variability) may be re-used to support Inclusion criterion 5 (assessment should be within 6 months of re-screening Visit 1). This option should only be used if additional screening spirometry cannot be performed or may represent a high risk in situation of natural disaster or public health crisis.

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

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

If applicable, safety procedures and sample collection may be performed according to the revised SoA in the Study Instruction for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis.

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

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

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow adverse events, concomitant medication, medical and COPD history, COPD treatment, COPD exacerbations, smoking status, supplemental oxygen status, healthcare resource utilization, compliance with eDiary questionnaires, and other information at deemed necessary by the Investigator to be reported and documented.

I 5 At-home or Remote Location IP Administration Instructions

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

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

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

I 5.2 At-home or Remote Location Self-Administration by the Patient or His/Her Caregiver

Prior to self IP administration, the investigator must assess the patient or his/her caregiver to determine whether they are capable of self-administration of IP. Once the patient or his/her caregiver is deemed appropriate for self-administration, he/she must receive appropriate training. All necessary supplies and instructions for administration of IP administration will be provided. More information related to the visit can be obtained via a telemedicine or during a home/remote visit.

I 6 Data Capture During Telemedicine or Home / Remote Visits

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

Appendix J Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization 14155 and European MDR 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1 for the list of sponsor medical devices.

J 1 Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

- An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved.
- An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

J 2 Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is an any serious adverse event that:

a. Led to death

b. Led to serious deterioration in the health of the participant, that either resulted in:

- A life-threatening illness or injury. The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

- A permanent impairment of a body structure or a body function.
- Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease (MDR 2017/745).

c. Led to fetal distress, fetal death, or a congenital anomaly or birth defect

SADE definition

- A SADE is defined as an adverse medical device effect that has resulted in any of the consequences characteristic of an SAE.
- Any medical device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition

- An USADE (also identified as UADE in United States Regulations 21 CFR 813.3), is defined as a serious adverse medical device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

J 3 Definition of Medical Device Deficiency

Medical Device Deficiency Definition

- A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

J 4 Recording and Follow-up of AE and/or SAE and Medical Device Deficiencies

AE, SAE, and Medical Device Deficiency Recording

- When an AE/SAE/medical device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/medical device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to AstraZeneca in lieu of completion of the Pregnancy Outcome Report/AE/SAE/medical device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by AstraZeneca. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to AstraZeneca.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For medical device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a medical device deficiency. This includes any amendment to the medical device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/medical device deficiency reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/medical device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products in his/her assessment.
- For each AE/SAE/medical device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/medical device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to AstraZeneca. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to AstraZeneca.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

MDCG 2020 Guidance

For the purpose of harmonizing reports, each SAE will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational[1] device or procedures.

1 Not related: Relationship to the device or procedures can be excluded when:

- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;

[1] Investigational device: any device object of the clinical investigation, including the comparators

- the serious event can be attributed to another cause (eg, an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2 Unlikely: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3 Possible: The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (eg, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4 Probable: The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

5 Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
- the investigational device or procedures are applied to;
- the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the participant is due to error in use;

- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Follow-up of AE/SAE/Medical Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by AstraZenecato elucidate the nature and/or causality of the AE/SAE/medical device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide AstraZeneca with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to AstraZeneca within 24 hours of receipt of the information.

J 5 Reporting of SAEs

SAE Reporting to AstraZeneca via Paper Data Collection Tool

- SAEs, pregnancies and overdose should primarily be reported in the EDC. Only report on paper form if EDC is unavailable. Fax cover sheet and Pregnancy/SAE Report Form (available in Site File) are to be used.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Site File.

J 6 Reporting of SADEs

SADE Reporting to AstraZeneca

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

- Any medical device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a medical device deficiency.
- The sponsor will review all medical device deficiencies and determine and document in writing whether they could have led to an SAE. These medical device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in Site File.

SIGNATURE PAGE

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23-Feb-2023 16:29 UTC	PPD	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.