**Title**: BURAN: Effects of Benralizumab on AiRwAy DyNamics in Severe Eosinophilic Asthma using Functional
Respiratory Imaging Parameters

**Study Code:** D3250R00107

**NCT number**: NCT05552508

**Date**: 08-Jan-2024

| **Clinical Study Protocol** | |
|---|---|
| Study Intervention | Benralizumab |
| Study Code | D3250R00107 |
| Version | 5.0 |
| Date | 08 January 2024 |

# BURAN: Effects of BenralizUmab on AiRwAy DyNamics in Severe Eosinophilic Asthma using Functional Respiratory Imaging Parameters

**Sponsor Name:**

Legal Registered Address: AstraZeneca AB, Södertälje, Sweden SE-15185

Manufacturer: AstraZeneca AB

**Regulatory Agency Identifier Number(s): EudraCT number - 2022-000152-11**

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

**Protocol Number: D3250R00107**

Amendment Number: 04

Study Intervention: Benralizumab

Study Phase: Phase 4

**Short Title: BURAN: BenralizUmab on AiRwAy DyNamics in Severe Eosinophilic Asthma using Functional Respiratory Imaging**

**Acronym**: **BURAN**

**Study Physician Name and Contact Information will be provided separately**

**International Co-ordinating Investigator:** PPD

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# VERSION HISTORY

Version 5.0 08 January 2024
Changes to the protocol are summarized below:

Version history: Clinical Study Protocol (CSP) Amendment Version 4.0 (23 March 2023) was updated to Version 5.0 (08 January 2024).

Section 1.1 Synopsis: It was clarified that benralizumab has proven efficacy and safety in Phase 3 **and 4** randomised clinical trials as well as studies using real world data. This was done to align with the text in Section 2.1 Rationale.

Section 1.1 Synopsis and Section 3 (Table 3): In the table of Objectives and Endpoints

1. Primary objective (change from baseline in siVaw from trimmed airways) and related endpoint (siVaw at TLC) were replaced with total mucus volume from untrimmed airways, and total mucus volume at TLC, respectively. This was done to reflect the importance of mucus in severe eosinophilic asthma (see also changes to Section 4.2 Scientific Rationale for Study Design). SiVaw at TLC was moved to secondary endpoints, and the remaining secondary endpoints were condensed to emphasize those relevant to airway occlusion by mucus, ie, total mucus plugs score, at TLC; total air trapping at FRC; trimmed distal iVaww at TLC; trimmed distal siVaw at TLC and FRC; and total iVlung at TLC and FRC. The secondary endpoints related to iRaw, iVlobe, BVX, IAD, ventilation mapping and ventilation/perfusion mapping, and their abbreviations in the table footnote, were deleted.
2. The breathing levels of FRI endpoint measurement (ie, at TLC, FRC or both) were elaborated.
3. From Secondary Objective 2 onwards, all FRI endpoints were moved to the table footnote. This was a minor edit to the protocol for clarity.
4. CCI [redacted]
5. Abbreviations were expanded for AE, FRC, IP, and TLC. This was a minor edit to the protocol for completeness.

Section 1.1 Synopsis (Number of Participants and Statistical Methods) and Section 9.2 Sample Size Determination:

1. CCI [redacted]
2. CCI [redacted]

Section 1. Synopsis (Statistical Methods) and Section 9.4.2 (Efficacy): The statistical

analyses methods were updated to align with the updated primary and secondary endpoints of the study.

Section 1. Synopsis (Statistical Methods) and Section 9.3 Populations for Analyses (Table 8), and Section 9.4.4 Other Analyses: Text was edited to clarify that all participants with baseline measurements who had taken at least 1 dose of the IP, irrespectively of whether they discontinued for reasons described in Section 7.1, were included in the baseline endpoints analysis set. This was done for clarity.

Section 2 Introduction and Section 11 References: The GINA, 2020 and GINA, 2021 references were updated to GINA, 2023, to keep abreast with the 2023 update of the Global Strategy for Asthma Management and Prevention.

Section 2.2 Background: The number of participants in the 24-week ANDHI trial was updated to 660, and the efficacy results from the trial were added to the protocol. This was done as per the IB update (Version 20.0).

Sections 2.3 Benefit/Risk Assessment and 2.3.1 Risk Assessment were edited and restructured to improve readability, reduce repetition of potential risk information, and align with the Sponsor's current position of the risk profile of benralizumab. In particular:

1. Table 2 Risk Assessment was deleted.
2. Serious hypersensitivity reactions was noted as identified risks of biologic therapy, including benralizumab.
3. Regarding the use of benralizumab in pregnant and lactating women, it was clarified that appropriate risk minimization measures have been implemented in the study protocol to address the risk of missing information. This was a minor edit for clarification, with no change to the risk assessment.
4. It was clarified that the clinical benefit demonstrated in clinical trials, combined with the overall safety profile of benralizumab, has established a positive benefit-risk profile for the approved severe asthma indication.

Section 4.2 Scientific Rationale for Study Design: The scientific rationale for the study design has been updated to emphasize the relevance of CT-based mucus plug scoring in severe eosinophilic asthma, the way in which FRI mucus volume assessment extends mucus plug scoring, and the connection with other FRI assessments. Text referencing specific airway volume as the primary endpoint has been updated to reference mucus volume instead.

Section 5.2.1 Exclusion criteria: Exclusion criterion 12 was updated to specify that participants who received Fasenra® any time prior to Visit 0 (V0) will also be excluded. This was done to clarify the prohibition of prior Fasenra® usage.

Section 6.2: Preparation/Handling/Storage/Accountability: The text was regarding unique IDs being printed in each IP kit was deleted. This was because this will not be done in this open-label study.

Section 6.5: Concomitant Therapy (Table 4 Restricted Medications) and 6.5.1 (Rescue Medications), the acronym for Single Maintenance and Reliever Therapy (SMART) was updated to Maintenance and Reliever Therapy (MART), as per updated in the updated GINA report of 2023. Additionally, in Table 5 Prohibited Medications, a minor edit was made to clarify that the use of "Any other" Investigational product is prohibited.

Section 8.1.1.1 FRI parameters: The list of FRI parameters was updated to include untrimmed total mucus volume at TLC as the primary endpoint, trimmed distal siVaw at TLC and FRC as secondary endpoints, and to specify which FRI endpoints were trimmed or untrimmed. The secondary endpoints related to iRaw, iVaw, iVlobe, BVX, IAD, ventilation mapping and Ventilation/perfusion mapping were deleted.

Section 8.1.1.2 Mucus plugging: Text describing the assessment of the newly added FRI parameter "untrimmed total mucus volume" was added.

Section 8.2.2 Vital signs: The timepoints for vital point measurements were updated to align with the SoA, and to make allowance for timepoints when vital signs may be measured as per Standard of Care. This was a minor edit for clarity.

Section 8.4.7 Reporting of Serious Adverse Events: Templatised text about the reference safety documents for active comparators was deleted, as there are no active comparators used in this study.

Section 8.5 Overdose: Templatised text referring the reader to the Sponsor's SOPs was deleted, as the site staff would not be using the Sponsor's internal SOPs.

Section 9.4.1 General Considerations: It was added that data may be log-transformed prior to analysis to reduce skewness of FRI parameters. This was done for clarity, in order to align with the assumptions of the planned model.

Section 9.4.2.1 Primary Objectives: The endpoint measure for the primary objective was updated as untrimmed total mucus volume at TLC, and the corresponding analysis method was updated.

Section 9.4.2.2 Secondary Objectives: The list of FRI parameters was updated to include untrimmed total mucus plugs score at TLC, untrimmed total air trapping at FRC, trimmed distal iVaww at TLC, trimmed distal siVaw at TLC and FRC, and untrimmed total iVlung at TLC and FRC as secondary endpoints. The secondary endpoints related to iRaw, iVlobe, BVX, IAD, ventilation mapping and ventilation/perfusion mapping were deleted. Furthermore, the corresponding analyses methods were revised.

Section 9.4.3 Safety: A statement about descriptive statistics for vital sign parameters measured at post-baseline visits was deleted. This was done to align the text in this section

with the Schedule of activities (Section 1.3).

Appendix B4 Data protection: this Appendix was updated to include additional text regarding data protection and personal data breaches to align with AstraZeneca's updated CSP template and regulatory requirements.

Appendix B5 Dissemination of Clinical Study Data: this Appendix was updated to include additional text to align with AstraZeneca's updated CSP template and regulatory requirements.

In addition to the edits above, format updates and typographical corrections were made throughout for correctness and consistency.

Version 4.0, 23 March 2023
Changes to the protocol are summarized below:

Version history: Clinical Study Protocol (CSP) Amendment Version 2.1 (07 September 2022) was corrected to Version 3.0 (12 September 2022).

Section 1.1 Synopsis: 'Short title' was replaced by 'Brief title' to align with AstraZeneca's updated CSP template.

Section 1.3 Schedule of Activities: 'COVID-19 vaccination status' procedure was removed as no longer considered a requirement due to changes in pandemic conditions.

Section 5.1 Inclusion Criteria:

- Inclusion Criterion 6: text was updated from 'Participants who have pre-bronchodilator FVC < 65% of predicted at Visit 0 (V0)' to 'Participants who have pre-bronchodilator $FEV_1/FVC \leq 70\%$ at Visit 0 (V0)' to identify patients with airflow obstruction, eosinophilic asthma and likely mucus plugging. A review of the spirometry data from patients in the SARP study (Tang et al, 2022) as well as other studies involving asthmatics with mucus plugs suggests that these patients tend to have lower $FEV_1$ levels as well as persistent airflow obstruction defined by $FEV_1/FVC$.
- Inclusion Criterion 10: this inclusion criterion was removed as it is no longer considered a requirement due to changes in pandemic conditions. Following deletion of IC 10, subsequent inclusion criteria numbering was updated in Section 5.1 and wherever referred to throughout the CSP.

Section 5.3.2 Alcohol, Tobacco, E-cigarettes and Marijuana: reference to EC#27 was updated with reference to EC#26, for correctness.

| |
|---|
| Section 6.5 Concomitant Therapy: text related to documentation of COVID-19 vaccines and vaccination status was deleted to reflect COVID-19 vaccination is no longer considered as a study requirement.<br><br>Section 7.1.1 Temporary Discontinuation: text related to temporary discontinuation of study treatment added.<br><br>Section 8.4.9 Medication Error, Drug Abuse, and Drug Misuse: text for medication error was revised, new subsections for timelines and definitions for medication errors, and drug abuse and drug misuse were added. Updates were made to align with AstraZeneca's updated CSP template and regulatory requirements.<br><br>Section 8.5 Overdose: redundant text pertinent to recording of overdose with and without symptoms was deleted, for correctness and consistency.<br><br>Section 8.6 Human Biological Samples: collection and handling of biological samples was specified to be conducted locally, to align with study procedures.<br><br>Appendix B1 Regulatory and Ethical Considerations: this Appendix was updated to include additional text for regulatory reporting requirements for serious breaches to align with AstraZeneca's updated CSP template and regulatory requirements.<br><br>Appendix B5 Dissemination of Clinical Study Data: this Appendix was amended to update the websites for posting of trial results summaries to align with AstraZeneca's updated CSP template and regulatory requirements.<br><br>Appendix B6 Data Quality Assurance: the period for retention of records and documents pertaining to the conduct of the study was amended from '15 years after study completion' to 'a minimum of 25 years after study archiving or as required by local regulations'. Updates were made to align with AstraZeneca's updated CSP template and regulatory requirements.<br><br>Appendix C4 Medication Error, Drug Abuse, and Drug Misuse: text for drug abuse and drug misuse was added to align with AstraZeneca's updated CSP template and regulatory requirements.<br><br>Format updates and typographical corrections were made throughout for correctness and consistency. |
| Version 3.0, 12 September 2022<br>Changes to the protocol are summarized below: |
| Long-acting muscarinic antagonist (LAMA) isolated or in fixed-dose combination is now allowed if initiation longer than 90 days and if dose will remain stable throughout the study |

duration. To reflect this change, the protocol was adjusted accordingly in Section 5.2.1 Exclusion - Criteria #14, Tables 4 and 5, Sections 8.1.1.1 and 8.1.2.

Symbicort SMART therapy was adjusted throughout the document to reflect all Budesonide/Formoterol Maintenance and Reliver Therapy (MART) options available.

Section 1.3 - Table 1 - Schedule of Activities – Lung function – language clarification on reversibility test schedule.

Section 2.3 – Benefit/Risk assessment – Risk minimization is updated to reflect the 1-hour observation period as recommended and is not mandatory based on current safety data available.

Section 5.1 – Criterion 17 and 18 adjusted to clarify requirements for female participants of childbearing potential.

Section 6.1.1 – Investigational Products – updated to comply with Good Manufacturing Practice (GMP) Annex 13

Section 6.7 – Rewritten to make it clear that the sponsor will not provide benralizumab upon study completion or early study withdrawal.

Section 8.4.2 - Follow-up of AEs and SAEs – Collection of the time when AE started and stopped is no longer required.

Some typographical, formatting, and grammatical corrections have been made.

Version 2.0, 03 March 2022

Changes to the protocol are summarized below:

Section 1.3 Schedule of Activities – COVID-19 test is not mandatory anymore at screening visit, and investigator site shall follow prevailing local guidelines for COVID-19 testing before any visits or procedures.

Section 5.1 Inclusion criteria #4 – Added criteria for sites in Belgium, due to reimbursement conditions, specifying that all participants in Belgium, irrespective of OCS-dependency, must have a blood eosinophil count $\geq$ 300 cells/µL at Visit 0 (V0).

Section 8.2.5 COVID-19 Testing – COVID-19 test is not mandatory anymore at screening visit, and investigator site shall follow prevailing local guidelines for COVID-19 testing before any visits or procedures. In addition, COVID-19 test results are no longer required to be recorded in the eCRF, but only in the ISF.

| |
|---|
| Some typographical, formatting, and grammatical corrections have been made.<br><br>Cross-references in the document have been updated to match new section numbering. |
| Version 1.0, 04 February 2022 |
| Initial creation |

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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:** BURAN: Effects of BenralizUmab on AiRwAy DyNamics in Severe Eosinophilic Asthma using Functional Respiratory Imaging Parameters

**Brief Title:** BURAN: BenralizUmab on AiRwAy DyNamics in Severe Eosinophilic Asthma using Functional Respiratory Imaging.

**Rationale:**

Benralizumab has proven efficacy and safety in Phase 3 and 4 randomized clinical trials as well as in studies using real world data; however, functional changes, mainly on airway dynamics, leading to the early clinical benefits are yet to be fully explored. Conventional lung function and patient-reported outcomes (PROs) do not fully describe extent of disease and mechanism of response to therapies. A deeper understanding of the short-term effects of benralizumab on airway dynamics could provide additional useful insights into clinically relevant improvements observed during the early stages of benralizumab treatment. Studies have demonstrated clinically relevant improvements in ventilation defect percent (VDP) as early as at 14-days post-benralizumab in participants with minimal changes in spirometry, suggesting that improvements in ventilatory heterogeneity may be detected sooner than (or in the absence of) improvements in spirometry (McIntosh et al., 2020).

Mucus plugs with eosinophilic inflammation are common and often persistent in patients with asthma. They may have a profound effect on pulmonary function and the development of exacerbations and may be visible on CT scans of most patients with severe asthma (Dunican et al., 2018). Since eosinophils are the major cell type found in the Charcot-Leyden crystals in mucus plugs of asthmatics, depletion of eosinophils should lead to a reduction in mucus plugging, resulting in improvement of airway patency and airflow distribution. Imaging of bronchial segments and scoring of mucus plugging is a well-accepted research tool in respiratory disease (Oguma et al., 2021). It has already been demonstrated that patients with high baseline mucus scores had significant improvements in VDP and asthma control post-benralizumab while those with low mucus scores did not (Kooner et al., 2021).

This mechanistic study will investigate the short-term benefits of sustained depletion of airway eosinophils by benralizumab on airway dynamics and mucus plugs in participants with severe eosinophilic asthma. The relationships between airway dynamic measurements and CCI [redacted] will also be explored, aiming to identify a link between CCI [redacted] with functional aspects at baseline, as well as the impact of treatment on these important patient-reported outcomes.

## Objectives and Endpoints

See footnote for abbreviations mentioned on the table below.

| Objectives | Endpoints[a] |
|---|---|
| Primary | |
| To describe the change from baseline in airway dynamics at week 13 following treatment with benralizumab, using total mucus volume measurements from untrimmed airways. | Unadjusted within subject difference in total mucus volume measured at TLC, calculated as the mean change from baseline (week 0) at week 13 (± 5 days). |
| Secondary | |
| 1. To describe the change from baseline in airway dynamics at week 13 following treatment with benralizumab, as measured by secondary FRI endpoints[b], irrespective of patient characteristics. | Unadjusted within subject difference in secondary FRI endpoints (total mucus plugs score at TLC; total air trapping at FRC; trimmed distal iVaww at TLC; trimmed distal siVaw at TLC and FRC; total iVlung at TLC and FRC), comparing baseline (week 0) to week 13 (± 5 days). |
| 2. To describe the relationship between airway dynamics and conventional lung function measurements, cross-sectionally (at week 0) and irrespective of patient characteristics. | Correlation between imaging endpoints (primary and secondary FRI endpoints[b] ) and pre-bronchodilator forced expiratory volume in 1 second (pre-BD $FEV_1$) at week 0.<br>Correlation between imaging endpoints (primary and secondary FRI endpoints[b]) and pre-bronchodilator forced vital capacity (pre-BD FVC) at week 0.<br>Scatter plots of primary and secondary FRI endpoints[a] versus conventional lung function measures (pre-BD $FEV_1$ and pre-BD FVC) at week 0.<br>Estimated increases in primary and secondary FRI endpoints[b] for every one percent increase in pre-BD $FEV_1$ and pre-BD FVC at week 0. |
| 3. To describe the relationship between changes from baseline (week 0) in airway dynamics and conventional lung function measurements at week 13, after accounting for baseline measurements of conventional lung function. | Correlation between the change from week 0 in imaging endpoints (primary and secondary FRI endpoints[b]) at week 13 and the change from week 0 in pre-BD $FEV_1$ at week 13 (± 5 days), overall and within subgroups conditional on the baseline value of pre-BD $FEV_1$.<br>Correlation between the change from week 0 in imaging endpoints (primary and secondary FRI endpoints[b]) at week 13 and the change from week 0 in pre-BD FVC at week 13 (± 5 days), overall and within subgroups conditional on the baseline value of pre-BD FVC. |

| | |
|---|---|
| | Scatter plots of changes from week 0 in primary and secondary FRI endpoints[b] at week 13 vs. changes from week 0 in conventional lung function measures (pre-BD $FEV_1$ and pre-BD FVC) at week 13.<br>Estimated change over time (week 13 vs. week 0) in primary and secondary FRI endpoints[b], with and without adjustment for conventional lung function measures (pre-BD $FEV_1$ and pre-BD FVC). |
| Safety | |
| To monitor the safety and tolerability of benralizumab. | Safety and tolerability will be evaluated in terms of AEs, Vital signs, and Clinical laboratory.<br>• Assessments related to AEs include:<br>– Occurrence/Frequency<br>– Relationship to IP or study procedure as assessed by investigator<br>– Intensity<br>– Seriousness<br>– Death<br>– AEs leading to discontinuation of IP<br>– Other significant AEs<br>– Time to onset<br>Vital signs parameters include systolic and diastolic blood pressure and heart rate. |

a. FRI endpoints are untrimmed unless otherwise specified.

b. The primary FRI endpoint is total mucus volume at TLC; secondary FRI endpoints for evaluation under secondary objectives include: total mucus plugs score at TLC, total air trapping at FRC; trimmed distal iVaww at TLC; trimmed distal siVaw at TLC and FRC; total iVlung at TLC and FRC; and total mucus plugs score at TLC.

AE = adverse event; $FEV_1$ = Forced expiratory volume in 1 second; FRC = Functional residual capacity; FRI = Functional Respiratory Imaging; FVC = Forced vital capacity; IP = investigational product; iVaww = Airway wall volume; iVlung = Lung volume; siVaw = Specific airway volume; TLC = Total Lung Capacity.

For CCI [redacted] objectives and endpoints, see Section 3 of the protocol.

**Overall Design**

This is an interventional, single group, open-label, uncontrolled, prospective, multicenter clinical trial.

**Disclosure Statement:** This is a single group treatment study with one arm that has no masking.

**Number of Participants:**

| | |
|---|---|
| Enrolled | Estimated 38 participants |
| Assigned | N/A (single-arm study) |
| Evaluable participants | Estimated 34 participants |
| Primary analysis population | Estimated 29 participants |

**Note**: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

**Intervention Groups and Duration:**

Each participant will be participating in the study for a minimum of 15 weeks (maximum of 23 weeks). Informed consent will be obtained from participants between 24 hours and 30 days prior to screening. Participants will be given instructions on how to adequately withhold their maintenance and rescue asthma medications prior to their screening visit. Once participants are enrolled into the study after screening, there will be a run-in period of 1 to 21 days (3 weeks) before Visit 1 (V1) at which time participants will undergo baseline assessments prior to receiving the first dose of benralizumab. There will be a total of three subcutaneously (SC) administered doses of benralizumab 30 mg given at weeks 0 (V1), 4 (V2), and 8 (V3). Final measurements will be taken at V4 at a minimum of 4 weeks to a maximum of 6 weeks after V3, followed by a 2-week follow-up period.

During the study, dose adjustment and dose interruption of benralizumab will not be permitted. Dosing can only be discontinued due to an AE per the Investigator's clinical judgement or unforeseen circumstances. Treatment rechallenge will not be permitted in this study and any participants who discontinue benralizumab will be considered a study withdrawal (see Section 7.1 for further details on criteria for discontinuation of study intervention).

**Data Monitoring Committee:** Not applicable

**Statistical Methods:**

Statistical methods used for the primary objective and secondary objective 1 will be univariate paired *t*-tests and mixed effects modelling. Scatter plots and correlation calculations will be used to assess the baseline association between all FRI parameters of interest and conventional lung function measures, $FEV_1$ and FVC, for the secondary objective 2. For secondary objective 2, linear regression models will also be fitted to quantify the baseline relationship between each FRI endpoint of interest and the conventional lung function measures. For secondary objective 3, scatter plots and correlation calculations will be used to assess the association between change from baseline in each FRI parameter and change from baseline in the conventional measures. For secondary objective 3, a linear model for FRI endpoints will also be estimated, both adjusted for $FEV_1$ and FVC and unadjusted for these measurements. These models will include an indicator variable for week 13 to quantify the change from baseline in FRI endpoints. Additional details and methods for other outcomes are provided in Section 9.4.2.

The sample size estimate required to detect a change from baseline in the primary endpoint (untrimmed total mucus volume at TLC) is 29 participants. This estimate is based on results from another study of a biologic treatment and FRI parameters, with the calculation details and corresponding assumptions enumerated in Section 9.2.

Safety analyses will be performed using the safety analysis set. Safety data will be presented using descriptive statistics unless otherwise specified.

The populations to be analyzed consist of:

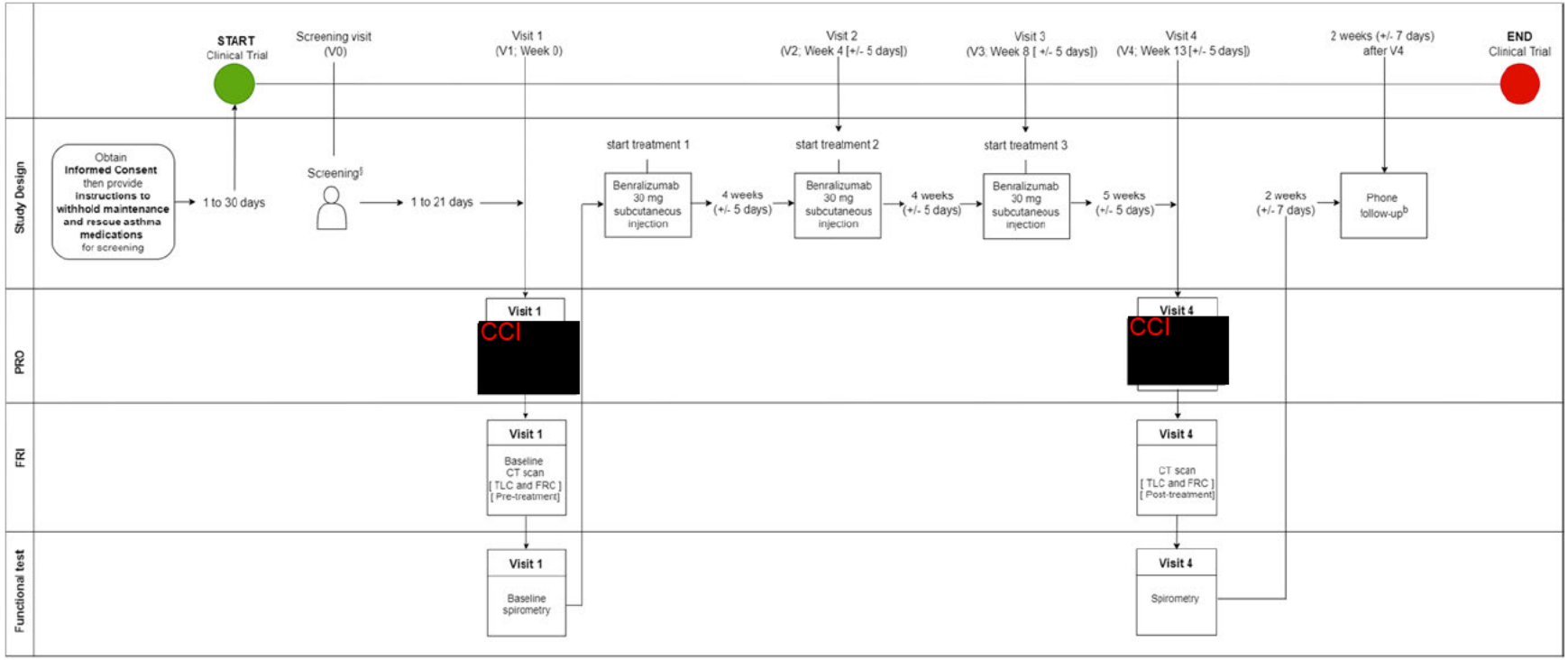
- Participants who completed the study per protocol definition and had no exacerbation during the study period (primary analysis population)
- All participants who completed the study per protocol definition
- Participants who completed baseline measurements at Visit 1 and had at least one dose of IP, irrespectively of whether they discontinued for reasons as described in Section 7.1 (the baseline endpoints analysis set).
- Subgroup analyses
  - Mucus plugging status: Participants with or without mucus plugs identified using CT scans (Section 8.1.1.2) taken at Visit 1 (week 0)
  - OCS dependency status: OCS-dependent and Non-OCS-dependent participants as defined by the inclusion criteria #4 (Section 5.1)

No interim analyses have been planned for this study.

See Section 9 for further details on the statistical methods and subgroup analyses.

## 1.2 Schema

**Figure 1 Study Design**




§: Screening visit includes ACQ-6, spirometry (with reversibility test if applicable), ECG and clinical laboratory testing. See Schedule of Activities for further details.

CCI [redacted]

[b] Patients will be evaluated on their medication status, AEs/SAEs and exacerbation history. Note that all safety parameters will be evaluated from pre-screening after informed consent is received until follow-up phone visit 5 or end of treatment follow-up visit for participants who discontinued early in the study.

CCI [redacted]; FRI = Functional Respiratory Imaging; PRO = patient-reported outcome; CCI [redacted]; V = visit.

## 1.3 Schedule of Activities

### Table 1 Schedule of Activities

| Procedure | Before Screening | Screening | Intervention period [Weeks] | | | | E/D | Follow-up Week 15[a] | Notes | Details in CSP Section or Appendix |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0 | 4 | 8 | 13 | | | | |
| Visit | N/A | 0 | 1 | 2 | 3 | 4 | N/A | 5 | | |
| Visit window (days)[b] | -30 to -1 before V0 | -21 before V1 | 0 | ±5 | ±5 | ±5 | ±7 | ±7 | | |
| **General procedures:** | | | | | | | | | | |
| Informed consent | X | | | | | | | | | Section 5.1 |
| Provide instructions for medication withhold for screening, Visit 1 and 4 | X | X | | | X | | | | Instructions to adequately withhold maintenance and rescue asthma medications prior to Visit 1 and 4. | Section 8.1.1 and 8.1.2 |
| Past and current medical/surgical and asthma history (includes history of COVID-19 infections) | | X | | | | | | | Substances: Drugs, alcohol, tobacco, e-cigarettes and marijuana | Section 5.1 and 5.2.1 |
| Medication status for asthma treatment | | X | | | | X | | | | Section 5.1 and 5.2.1 |
| Inclusion and exclusion criteria (including smoking status) | | X | | | | | | | | Section 5.1 and 5.2.1 |
| Review exacerbations status and current medication for exclusion criteria | | | X | | | | | | | Section 5.2.2 |
| Demography | | X | | | | | | | | Section 5.1 |
| Height and weight | | X | | | | | | | | |
| 12-lead ECG | | X | | | | | | | | Section 8.2.3 |

| Procedure | Before Screening | Screening | Intervention period [Weeks] | | | | E/D | Follow-up Week 15[a] | Notes | Details in CSP Section or Appendix |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0 | 4 | 8 | 13 | | | | |
| Visit | N/A | 0 | 1 | 2 | 3 | 4 | N/A | 5 | | |
| Visit window (days)[b] | -30 to -1 before V0 | -21 before V1 | 0 | ±5 | ±5 | ±5 | ±7 | ±7 | | |
| **Laboratory assessments:** | | | | | | | | | | |
| COVID-19 test[c] | Before any visits or procedures as per prevailing local guidelines for COVID-19 testing | | | | | | | | | Section 5.1, 5.2.1, 5.5.4 and 8.2.5 |
| Clinical laboratory assessments (including blood eosinophils) | | X | | | | | | | | Section 8.2.4 |
| Serum pregnancy test (WOCBP only) | | X | | | | | | | | Section 5.1, 5.2.1, 8.2.4.1 and 8.4.8 |
| FSH (women < 50 years) | | X | | | | | | | | Section 5.1, 5.2.1 and 8.2.4.1 |
| Urine pregnancy test (WOCBP only) | | | X[d] | X[d] | X[d] | X[d] | | | For Visit 1 and 4, pregnancy status must be checked before CT scan. A positive urine test result must be confirmed with a serum pregnancy test. | Section 5.1, 5.2.1, 8.2.4.1 and 8.4.8 |

| Procedure | Before Screening | Screening | Intervention period [Weeks] | | | | E/D | Follow-up Week 15[a] | Notes | Details in CSP Section or Appendix |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0 | 4 | 8 | 13 | | | | |
| Visit | N/A | 0 | 1 | 2 | 3 | 4 | N/A | 5 | | |
| Visit window (days)[b] | -30 to -1 before V0 | -21 before V1 | 0 | ±5 | ±5 | ±5 | ±7 | ±7 | | |
| **Safety assessments:** | | | | | | | | | | |
| Physical examination | | X | X | X | X | X | X | | | Section 8.2.1 and 8.4.5 |
| Adverse Events (AE)[e] | | X | X | X | X | X | X | X | AEs should be reported from first dose of IP to end of study. SAEs should be reported from signing of ICF. | Section 8.4 |
| History of asthma exacerbation[e] | X | X | X | X | X | X | X | X | | Section 8.3 and 8.4.6 |
| Asthma Medication (maintenance and rescue) | | X | X | X | X | X | X | X | Oral corticosteroids should also be documented in the eCRF. | Section 5.2.1 and 6.5 |
| Concomitant medication | | X | | | | X | | X | | Section 5.2.1 and 6.5 |
| Vital signs | | X | | | | | X | | | Section 8.2.2 |
| **Patient Reported Outcomes Assessments:** | | | | | | | | | | |
| CCI [redacted] | | | | | | | | | | |

| Procedure | Before Screening | Screening | Intervention period [Weeks] | | | | E/D | Follow-up Week 15[a] | Notes | Details in CSP Section or Appendix |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0 | 4 | 8 | 13 | | | | |
| Visit | N/A | 0 | 1 | 2 | 3 | 4 | N/A | 5 | | |
| Visit window (days)[b] | -30 to -1 before V0 | -21 before V1 | 0 | ±5 | ±5 | ±5 | ±7 | ±7 | | |
| **FRI assessment:** | | | | | | | | | | |
| CT scan [h,i,j,k] | | | X | | | X | | | A urine pregnancy test should be done prior to all CT scan procedures. | Section 8.1.1 |
| **Lung function assessments:** | | | | | | | | | | |
| Spirometry (pre-bronchodilator) - reversibility test (post-bronchodilator) to also be performed if required [k,l] | | X | | | | | | | | Section 5.1 and 8.1.2 |
| Spirometry (pre-bronchodilator)[k,m] | | | X | | | X | | | Spirometry should be done after CT scan procedure. | Section 8.1.2 |
| **Investigational Product administration:** | | | | | | | | | | |
| Study intervention | | | X[n] | X[n] | X[n] | | | | | Section 6.2 |

[a] Only for participants who completed 3 doses of IP.
[b] Any rescheduling of visits beyond the visit window indicated in this Schedule of Activity should be an exception and the reason should be recorded in the ISF
[c] Each investigator site shall follow prevailing local guidelines for COVID-19 testing before any visits or procedures. Participants are considered as having positive COVID-19 test when they fulfill the criteria defined as per aforementioned guidelines. If a patient presents with a positive COVID-19 test result, Visit 0 may be rescheduled as per guidance in Section 5.4. If a patient presents with a positive COVID-19 test result at any time, visits may be rescheduled as per guidance in Section 5.5.4.
[d] A urine pregnancy test must be done before all study assessments (PROs, CT scan and spirometry test). All study assessments and administration of benralizumab must be stopped if a participant has a positive urine pregnancy test.
[e] If a participant experiences an acute exacerbation or respiratory tract infection during the study, refer to Section 8.3 for further details.
[f] [redacted]
[g] [redacted]
[h] CT scans should be conducted using the low radiation dose scanning protocol as approved by the central vendor during the certification process for the CT scanning procedures prior to study center activation for the study.
[i] CT scans will be taken at two breathing levels: Total lung capacity (TLC) and functional residual capacity (FRC).

[j] All CT scans will be conducted with respiratory gating using equipment (CE-marked) provided by the central vendor.
[k] Maintenance and rescue asthma medications need to be adequately withheld prior to Visit 0, 1 and 4 for the spirometry testing and/or CT procedures that will be scheduled during these visits (see Section 8.1.1 for CT scan procedures and Section 8.1.2 for spirometry procedures).
[l] Reversibility testing should be conducted if participants do not have historical documentation (medical records) of reversibility post-BD. Participants will need either documented reversibility post-BD either historically (medical records) or at screening visit to fulfil inclusion criterion #2 (see Section 5.1).
[m] Spirometry test conducted during Visit 1 and 4 should always be performed after the participants undergo the CT scan procedure. If not feasible, there should be at least 30 min between the spirometry test and subsequent CT scan procedure.
[n] For WOCBP only, study intervention should only be administered after confirmation with a negative urine pregnancy test.
CCI AE = adverse event; CCI ; BD = bronchodilator; CT = computed tomography; CSP = Clinical Study Protocol; ECG = electrocardiogram; eCRF = electronic case report form; E/D = Early study intervention discontinuation; HIV = Immunodeficiency virus; ICF = informed consent form; IP = investigational product; N/A = not applicable; SAE = serious adverse event; CCI ; WOCBP = women of childbearing potential.

# 2 INTRODUCTION

Asthma is a chronic inflammatory airway disorder caused by the interaction of genetic and environmental factors. It is characterized by widespread, variable, reversible airflow obstruction, airway inflammation, excessive mucus production, and airway hyper-responsiveness that led to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing (The Collaborative Study on the Genetics of Asthma, 1997; GINA, 2023).

The current guidance on the management of patients with asthma is a stepwise intensification of a daily maintenance regimen primarily centered around the combination of inhaled corticosteroids (ICS) and long-acting β2 agonists (LABA) (GINA, 2023, GINA, 2021). In patients with moderately severe asthma, an add-on of tiotropium or leukotriene receptor antagonists (LTRA) is recommended, while the add-on of tiotropium or anti-immunoglobulin E (IgE), anti-interleukin-5/5 receptor (anti-IL5/5R), or anti-IL4R is recommended for those with severe asthma (GINA, 2023).

A review of the clinical responses following treatment with currently available asthma therapies uncovered variability that may be related, in part, to distinctive inflammatory phenotypes (Wenzel, 2012). Noteworthy is asthma associated with eosinophilic inflammation in the airway (also referred to as eosinophilic asthma) representing approximately 40% to 60% of patients with asthma; these patients exhibit a degree of eosinophilia associated with clinical severity including the risk of asthma exacerbations (Bousquet et al., 1990; Louis et al., 2000; Di Franco et al., 2003; Scott and Wardlaw, 2006, Simpson et al., 2006; Zhang and Wenzel, 2007). Also of interest is the observed reduction in the frequency of asthma exacerbations when conventional ICS-based asthma therapy was adjusted according to the degree of sputum eosinophils as a biomarker of disease activity in prospective trials (Green et al., 2002; Jayaram et al., 2006).

IL-5 is a cytokine factor essential for eosinophil trafficking and survival (Molfino et al., 2011). Benralizumab is an anti-IL5R monoclonal antibody developed as add-on therapy for patients with severe eosinophilic asthma.

## 2.1 Study Rationale

To date, benralizumab has proven efficacy and safety in both randomized clinical trials (Phase 3 and 4) as well as in studies using real-world data. Functional changes on airway dynamics and their correlation to the clinical benefits measured by conventional lung function and patient-reported outcomes (PROs) following treatment with benralizumab, have yet to be fully explored.

Studies utilizing 129Xe magnetic resonance imaging (MRI) demonstrated clinically relevant VDP improvements as early as at 14-days post-benralizumab in participants with minimal

changes in spirometry measures (McIntosh et al., 2020).

In this study, Functional Respiratory Imaging (FRI) will be used to measure changes in airway dynamics. FRI is a relatively novel quantitative method to measure biological responses to therapeutic interventions using a combination of high-resolution computed tomography (CT) and computational fluid dynamics (CFD). FRI provides detailed visualization and evaluation of the lungs and airway structures, allowing for an in-depth description of baseline lung health and level of deterioration and a better understanding of post-treatment effects. By assessing changes close to the site of action of the intervention, the method is more sensitive (higher effect size) compared with standard lung function tests (De Backer et al., 2012a). Several clinical trials in patients with asthma (De Backer et al., 2008; Vos et al., 2013; De Backer et al., 2015) and chronic obstructive pulmonary disease (COPD) showed significant correlations between the change in forced expiratory volume in 1 second ($FEV_1$), other pulmonary function test parameters or asthma control, and the change in both image-based volume and/or airway resistance following bronchodilation or resolution of exacerbation (De Backer et al., 2011; Vos et al., 2016; De Backer et al., 2018; Van Geffen et al., 2018). The background variance of well controlled imaging such as FRI is lower relative to pulmonary function testing due to the exclusion of confounding factors such as upper airway properties, patient effort, and coaching. This means that FRI has enhanced sensitivity (better signal to noise ratio) compared with conventional spirometry (Ides et al., 2012; De Backer et al., 2013).

In addition to bronchoconstriction and airway thickening, mucus plugging is common and often persistent in patients with asthma and seen on CT scans of most patients. Eosinophils are the major cell type found in the Charcot-Leyden crystals in mucus plugs of asthmatics. Mucus plugs with eosinophilic inflammation may have a profound effect on pulmonary function and the development of exacerbations, and imaging of bronchial segments and scoring of mucus plugging is a well-accepted research tool in respiratory disease (Oguma et al., 2021).

Depletion of eosinophils should lead to a reduction in mucus plugging on imaging and improvement of airway patency and airflow distribution. Kooner et al. demonstrated that patients with high baseline mucus score had significant improvements in VDP and asthma control post-benralizumab while participants with low mucus score did not (Kooner et al., 2021).

Ongoing trials like the CHINOOK study will also evaluate the relationship between any observed effects on airway remodeling, improvements in lung physiology and airway dynamics in response to benralizumab; however, this study is primarily focused on the impact on airway remodeling by morphological and histological measures in subjects with severe eosinophilic asthma (NCT03953300; ClinicalTrials.Gov).

This mechanistic study will thus investigate the short-term benefits of sustained depletion of airway eosinophils by benralizumab on airway dynamics and mucus plugs in participants with

severe eosinophilic asthma. The relationships between airway dynamic measurements and CCI CCI will also be explored, aiming to identify a link between CCI with functional parameters measured at baseline and following treatment with benralizumab.

## 2.2 Background

Benralizumab is currently approved for clinical use by the United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA) as add-on maintenance treatment of patients with severe asthma and with an eosinophilic phenotype. It is a humanized, afucosylated, monoclonal antibody against the IL-5R α subunit that induces direct, rapid, and near-complete depletion of eosinophils in blood, airway tissue, and bone marrow through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) (Tan et al., 2016). Natural killer cells are involved in this apoptotic process resulting in controlled eosinophilic elimination (Kolbeck et al., 2010; Pham et al., 2016).

The efficacy and safety of benralizumab has been evaluated in four phase 3 randomized controlled clinical trials. Benralizumab significantly decreased the rate of annual exacerbations and improved $FEV_1$, compared with placebo, in patients with severe uncontrolled asthma who were receiving high-dose inhaled corticosteroids and long-acting $\beta_2$ agonists in the SIROCCO (Bleecker et al., 2016) and CALIMA (FitzGerald et al., 2016) trials.

In the 24-week ANDHI trial (n = 660), benralizumab significantly reduced exacerbation risk compared with placebo in addition to statistically significant improvements from baseline to week 24 in CCI versus placebo. Benralizumab also improved pulmonary function as measured by change from baseline in pre-BD FEV1 (Harrison et al., 2021, Investigator's Brochure). The rate of AEs was similar between the benralizumab and placebo groups (Harrison et al., 2021). This analysis included patients with an eosinophilic phenotype defined as an EOS count of ≥ 150/µl plus at least one of the following: maintenance OCS, nasal polyps, FVC < 65% predicted, 3 or more exacerbations in the prior year and adult onset of disease (Harrison et al., 2021).

In the 28-week ZONDA trial, benralizumab significantly reduced the need for oral corticosteroids as well as the rate of asthma exacerbations in an OCS dependent population when compared to placebo (Nair et al., 2017).

The efficacy and safety of benralizumab was also evaluated in open label trials, such as the open-label extension trials, MELTEMI (Korn et al., 2021) and PONENTE (Menzies-Gow et al., 2021), with both efficacy and safety results consistent with the pivotal trials.

Nevertheless, the shorter-term effects of benralizumab on airway dynamics remain to be fully elucidated. A deeper understanding of this could provide additional useful insights into the

clinically relevant improvements observed early in the course of treatment.

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

## 2.3 Benefit/Risk Assessment

The clinical benefit-risk balance for benralizumab was evaluated by taking into consideration data from preclinical and clinical studies, as well as a review of the available information for monoclonal antibodies that are approved for and are in development for the treatment of severe asthma. Benralizumab has been well tolerated, with the most frequently observed AEs from the Phase 3 controlled studies being generally reflective of a severe asthma patient population.

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

### 2.3.1 Risk Assessment

- For the following potential risks of clinical significance, summary of data related to these risks, and corresponding mitigation strategies for the investigational product (IP), benralizumab, may be found in the Investigator's Brochure.Serious hypersensitivity reactions (including anaphylaxis) are identified risks of biologic therapy, including benralizumab. Anaphylaxis may be life-threatening. Risk minimization recommends a minimum of a 1-hour observation period at the clinical site 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 include decreased drug efficacy and hypersensitivity reactions. There was no apparent impact of ADA on overall benralizumab safety or efficacy in the phase 3 trials.
- 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. There were no reports of helminth infection in the phase 3 asthma exacerbation studies.
- 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 (ie, pro-tumorigenic versus antitumorigenic) of eosinophil recruitment and accumulation into tumors are unclear (Jacobsen et al., 2012).
- Serious infections have been reported for benralizumab. The incidence of serious infections was similar across groups in the phase 3 asthma exacerbation studies. A relationship between eosinophil depletion and serious infection has not been established.
- Information regarding the use of benralizumab in pregnant and lactating women is currently missing. Appropriate risk minimization measures have been implemented in the study protocol (see Section 1.3, 5.2 and 7.1).

The clinical benefit demonstrated in clinical trials, combined with the overall safety profile of benralizumab has established a positive benefit-risk profile for the approved severe asthma indication. Risk minimization measures include the exclusion of participants with allergy or reaction to any component of the benralizumab formulation, untreated helminth parasitic infection and active or recent malignancy, while concurrently performing routine pharmacovigilance activities.

Risks of the study design are those associated with computed tomography (CT). In clinical practice, patients with asthma are not subjected to many high-resolution CT scans. As such, undergoing the CT procedure during this study may result in a benign or incidental finding. The use of CT also involves ionizing radiation that increases the risk of radiogenic tumors in participants and may also pose a risk to embryo fetal development and infant. Steps will be taken to minimize these risks including the exclusion of pregnant and lactating women in the study. Further information on the steps taken to reduce radiation exposure are detailed below. The CT procedures incorporated into this study design are aligned with the directives presented in the European Union (EU) guidance (Directorate-General – Environment, nuclear safety and civil protection, 1998a). Participants will be informed of the risks associated with the CT procedure before entering the study.

In this study, extra attention will be paid to reduce radiation by providing low radiation scanning protocols tailored to the specific scanner available at participating sites. Low radiation scanning protocol guidance will be provided to sites before any subject scan visits. Participating study centers will be required to set up a study-allocated CT scanner with a low radiation scanning protocol and conduct a phantom scan using this protocol. The phantom scan will be sent to a central vendor supporting this study for FRI analysis for review and confirmation for the low radiation CT scanner settings. All study team personnel involved in the CT scanning procedure will also undergo training to ensure quality and consistency of the high-resolution CT scans are maintained across study centers. Study centers will only be certified for the CT scanning procedure after the phantom scan is approved by the central vendor and all relevant study team personnel have successfully completed their training.

Specifically, the amount of radiation exposure for participants in this study is dependent on the scanner used. The software CT-expo is used to give an estimation of the radiation dose a patient will get from a FRC/TLC CT scan. CT-expo's calculations are based on computational methods which were used to evaluate the data collected in both German surveys on CT exposure practice in 1999 and 2002 (Stamm and Nagel, 2014). A comprehensive description of these methods can be found in the book 'Radiation Exposure in Computed Tomography' (Nagel and Walter, 2002). Based on a selection of CT scanner brands and models from four manufacturers, the estimated radiation exposure using the low radiation scanning protocols recommended for this study can be found on Table S1 (Appendix A). Specific settings that were used in CT-expo are described on Table S2 (Appendix A).

The average effective dose for a high-resolution CT scan that will be conducted for this study averaged over all scanner types mentioned in Table S1 (Appendix A) is 1.945 mSv. The average estimated radiation exposure received by participants in this study for four high-resolution CT scans will be 7.78 mSv (based on the scanner brands and models in Table S1 [Appendix A]; note this calculation is dependent on body size and composition). This dose is within the accepted radiation dose range for biological research (1 to 10 milli Sieverts;

Directorate-General – Environment, nuclear safety and civil protection 1998a).

It is noteworthy that while a high-resolution CT scan taken with the recommended low radiation protocol in this study is higher than a standard chest x-ray or mammogram at 0.02 mSv and 0.13 mSv respectively according to the US Environmental Protection Agency (US Environmental Protection Agency, 2021a), the average estimated radiation exposure received by participants in this study for four high-resolution CT scans at 7.78 mSv (based on the scanner brands and models in Table S1 [Appendix A]) is approximately 4 times lower than four standard chest CT scans which would expose a person to 32 mSv of radiation (8 mSv per scan [US Environmental Protection Agency, 2021b]).

An average US citizen receives an annual natural background radiation exposure from natural sources of 3.1 mSv (United States Nuclear Regulatory Commission, 2017). Participants completing this study will therefore receive an equivalent of 2.5 years background radiation based on the average estimated radiation exposure in Table S1 (Appendix A). Based on the estimated total amount of radiation exposure for each participant, the potential benefits of the study are also expected to be Category IIB following the European Union (EU) guidance document (Directorate-General – Environment, nuclear safety and civil protection 1998b) targeting the diagnosis, cure, or prevention of disease.

Further calculations on the relative risk increase were conducted and demonstrated a relative risk increase of 0.033% for the 7.78 mSv received from all scans in the current study, based on the detriment adjusted nominal risk coefficient for an adult at 4.2% per Sv as published by the International Commission on Radiological Protection (ICRP) in 2007 (ICRP, 2007).

### 2.3.2 Benefit Assessment

Benefits of benralizumab include clinically and statistically significant reductions in annual exacerbation rate, improved lung function, and improved symptom control. These would in turn result in better health-related quality of life and lower systemic steroid exposure. Participants in this study will also contribute to furthering the understanding of the short-term benefits of sustained depletion of airway eosinophils by benralizumab on airway dynamics and mucus plugs in severe eosinophilic asthma.

### 2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with benralizumab are justified by the anticipated benefits that may be afforded to participants with severe asthma and with an eosinophilic phenotype.

# 3 OBJECTIVES AND OUTCOME MEASURES

## Table 2 Objectives and Outcome Measures

See footnote for abbreviations mentioned on the table below.

| Objectives | Outcome measures[a] |
|---|---|
| Primary | |
| To describe the change from baseline in airway dynamics after 13 weeks following treatment with benralizumab, using total mucus volume (specific airway volume) measurements from untrimmed airways. | Unadjusted mean within subject difference in total mucus volume measured at TLC, calculated as the mean change from baseline (week 0) at week 13 (± 5 days). |
| Secondary | |
| 1. To describe the change from baseline in airway dynamics at week 13 following treatment with benralizumab, as measured by secondary FRI endpoints[b], irrespective of patient characteristics. | Unadjusted mean within subject difference in secondary FRI endpoints (total mucus plugs score at TLC; total air trapping at FRC; trimmed distal iVaww at TLC; trimmed distal siVaw at TLC and FRC; total iVlung at TLC and FRC), comparing baseline (week 0) to week 13 (± 5 days). |
| 2. To describe the relationship between airway dynamics and conventional lung function measurements, cross-sectionally (at week 0) and irrespective of patient characteristics. | Correlation between imaging endpoints (primary and secondary FRI endpoints[b] ) and pre-bronchodilator forced expiratory volume in 1 second (pre-BD $FEV_1$) at week 0.<br>Correlation between imaging endpoints (primary and secondary FRI endpoints[b] ) and pre-bronchodilator forced vital capacity (pre-BD FVC) at week 0.<br>Scatter plots of primary and secondary FRI endpoints[b] and mucus plugs score versus conventional lung function measures (pre-BD $FEV_1$ and pre-BD FVC) at week 0.<br>Estimated increases in primary and secondary FRI endpoints[b] and mucus plugs score for every one percent increase in pre-BD $FEV_1$ and pre-BD FVC at week 0. |
| 3. To describe the relationship between changes from baseline (week 0) in airway dynamics and conventional lung function measurements at week 13, after accounting for baseline measurements of conventional lung function. | Correlation between the change from week 0 in imaging endpoints (primary and secondary FRI endpoints[b]) at week 13 and the change from week 0 in pre-BD $FEV_1$ at week 13 (± 5 days), overall and within subgroups conditional on the baseline value of pre-BD $FEV_1$.<br>Correlation between the change from week 0 in imaging endpoints (primary and secondary FRI endpoints[b]) at week 13 and the change from week 0 in pre-BD FVC at week 13 (± 5 days), overall and within subgroups conditional on the baseline value of pre-BD FVC. |

| | |
|---|---|
| | Scatter plots of changes from week 0 in primary and secondary FRI endpoints[b] and mucus plugs score at week 13 vs. changes from week 0 in conventional lung function measures (pre-BD $FEV_1$ and pre-BD FVC) at week 13.<br>Estimated change over time (week 13 vs. week 0) in primary and secondary FRI endpoints[ab], with and without adjustment for conventional lung function measures (pre-BD $FEV_1$ and pre-BD FVC). |
| Safety | |
| To monitor the safety and tolerability of benralizumab. | Safety and tolerability will be evaluated in terms of AEs, Vital signs, and Clinical laboratory.<br>• Assessments related to AEs include:<br>– Occurrence/Frequency<br>– Relationship to IP or study procedure as assessed by investigator<br>– Intensity<br>– Seriousness<br>– Death<br>– AEs leading to discontinuation of IP<br>– Other significant AEs<br>– Time to onset<br>Vital signs parameters include systolic and diastolic blood pressure, and heart rate. |
| CCI | |

CCI [redacted]

CCI

a. FRI endpoints are untrimmed unless otherwise specified (Section 8.1.1.1).

b. The primary FRI endpoint is total mucus volume at TLC; secondary FRI endpoints for evaluation under secondary objectives include total mucus plugs score at TLC, total air trapping at FRC; trimmed distal iVaww at TLC; trimmed distal siVaw at TLC and FRC; total iVlung at TLC and FRC; and total mucus plugs score at TLC.

CCI ; AE = adverse event; CCI ; $FEV_1$ = Forced expiratory volume in 1 second; FRC = Functional residual capacity; FRI = Functional Respiratory Imaging; FVC = Forced vital capacity; IP = investigational product; iVaww = Airway wall volume, iVlung = Lung volume, CCI ; CCI ; CCI ; siVaw = Specific airway volume; TLC = Total Lung Capacity.

# 4 STUDY DESIGN

## 4.1 Overall Design

This is an interventional single group, open-label, uncontrolled, prospective, multicenter clinical trial.

The study will be conducted in male and female participants ≥18 years old with established severe eosinophilic asthma, as defined by ERS/ATS clinical guidelines (Chung et al., 2014), inadequately controlled by treatment with ICS-LABA with or without oral corticosteroids (OCS) or other asthma controller medications.

There will be no study intervention assignment applied as this is a single group study.

Each participant will participate in the study for a minimum of 15 weeks and up to 23 weeks from the time when informed consent is obtained through to end of study, inclusive of study follow-up. The following are the sequence and duration of study periods:

- Informed consent and instructions for withholding maintenance and rescue asthma medications for screening (24 hours to 30 days prior to screening)
- Screening visit (V0)
- Visit 1 (V1; week 0; within 1 to 21 days of screening)
- Visit 2 (V2; week 4 ± 5 days)
- Visit 3 (V3; week 8 ± 5 days)
- Visit 4 (V4; week 13 ± 5 days)
- Follow-up (2 weeks [± 7 days] after V4) - Phone call follow-up

Refer to Table 1 for further information on the Schedule of Activities (SoA) to be performed throughout the study.

Patients will be discharged from the study after the phone call follow-up is completed. This study will not be extended and there will be no roll-over studies. Refer to Section 6.7 for further information on intervention after the end of the study.

## 4.2 Scientific Rationale for Study Design

*Single-arm design*

The decision to conduct a single-arm study instead of a placebo-controlled study was based on several factors.

Firstly, benralizumab has been approved in all major markets, and its efficacy is established in the target patient population. While it is of scientific value to add a placebo arm to this study, this addition in the context of a phase IV study in a population prone to exacerbations, and

with the availability of other biologics for asthma, will complicate study enrolment and increase the number of patients enrolled on both arms, thus delaying the availability of important results from this study. Furthermore, having a placebo arm would be unnecessarily exposing patients to radiation through the study procedure.

Next, as previously discussed, it is noteworthy that FRI endpoints, unlike those derived from spirometry are not influenced by patient effort or muscle force, and are thus less likely to change due to a non-disease-related placebo effect. Several studies in asthma and COPD have demonstrated very low variability in FRI parameters when patients are not subjected to an intervention or when imaged after equivalent maintenance medication withhold periods (De Backer et al., 2012a; De Backer et al., 2016; De Backer et al., 2018; Langton et al., 2019).

A study in an asthmatic population showed no change in airway volumes (siVaw) in repeated high resolution CT scans after 3 to 7 days when equivalent wash-out periods were observed (De Backer et al., 2016). Another study of patients with severe asthma who underwent bronchial thermoplasty also demonstrated that airways in the untreated lung did not change significantly after 4 weeks (Langton et al., 2019). Subsequent variability analysis was undertaken on untreated subjects from a previous double-blind placebo-controlled study on the longitudinal change in FRI endpoints to inform expectations for endpoint progression in untreated patients (data on file). FRI endpoints were measured at weeks 0 and 12 among 22 placebo subjects selected based on similar characteristics to that in the current study (sputum eosinophilia and persistent, moderate-to-severe asthma). In the placebo group, siVaw changed (decreased) an average of -3.46% between weeks 0 and 12, with a 95% CI of (-7.50%, 0.584%), suggesting that subjects not receiving treatment are likely to exhibit stable or declining endpoint values. It should be noted that measures will also be taken during the CT image acquisition process to ensure variability is reduced during this procedure. This includes, but is not limited to, the use of phantom scans to ensure every site adheres to specific scanning protocols provided to them. These quality assurance measures will further improve the signal-to-noise ratio.

Apart from the above, previous studies have reported a worsening in airway endpoints in patients treated with placebo. This was observed in a placebo-controlled cross-over study assessing the effect of budesonide/formoterol in patients with COPD (De Backer et al., 2012a), as well as in another placebo-controlled cross-over study assessing the effect of glycopyrrolate/formoterol fumarate in patients with COPD (De Backer et al., 2018). Therefore, the proposal to study within-patient changes from baseline in a single-arm study may perhaps be a more conservative approach compared with a placebo-controlled study design.

Taking the above rationales into consideration, the proposal of a single-arm study design may be the most appropriate approach to meet the study aims and intention. Placebo data in

patients with severe asthma will become available from other studies of biologics in severe asthma (NCT04400318) and could be used as a placebo group in future post-hoc analysis.

Correlation analysis conducted by De Backer and colleagues on both patients with asthma (n = 79) and those with COPD (n = 49) suggest that the effect size of FRI outcomes in response to respiratory treatment in asthma and COPD appear to be three-to-four times larger than those in $FEV_1$, the current gold standard efficacy endpoint (De Backer et al., 2015). The investigators concluded that FRI may be a good tool for evaluating the potentially subtle changes in lung function caused by anti-inflammatory compounds (De Backer et al., 2015). FRI studies in patients with severe asthma following treatment with other biologics are ongoing and data are not available presently.

CT-based mucus plug scoring has been shown to be positively associated with asthma linked eosinophilia (Dunican et al., 2018). Moreover, in patients with asthma, the presence of mucus plugs in four or more lung segments occurred in 67% of patients with $FEV_1$ (percent predicted) of less than 60%, 19% of patients with $FEV_1$ from 60%-80%, and 6% of patients with $FEV_1$ greater than 80% (Dunican et al., 2018). These results suggest that airway occlusion by mucus is plausibly a mechanism underlying airflow obstruction in eosinophilic asthma. Therefore, it could be speculated that benralizumab-mediated eosinophil depletion in severe eosinophilic asthmatics may reduce mucus burden and correspondingly, the degree of airway obstruction.

Current methods for mucus plug scoring are discrete counts that disregard mucus plug size. However, a novel method has been developed as part of FRI that extends mucus plug scoring by measuring the volume of mucus plugs in the airways visible via CT imaging, thereby accounting for variations in mucus plug size through this assessment. Given the established relationship between mucus plugs and airway obstruction, it is also plausible that reduced mucus volume will result in reduced air trapping and increased airway volume as assessed via FRI. These changes may lead to improvements in the participant's lung function and patient-reported outcomes (PROs), ultimately allowing the participant to breathe more easily and thus feel better and experience a better quality of life. A clinically meaningful change in the primary endpoint would be a significant change in total untrimmed mucus volume at week 13 from baseline after treatment with benralizumab. Significant changes in $FEV_1$, forced vital capacity (FVC) and scores from CCI [redacted], and positive correlations between these changes and the changes in the primary endpoint would further reflect and support the clinically meaningful improvements in outcomes under benralizumab. It will also allow the results from the current study to be put into context with previous or future findings from studies on benralizumab treatment (see below for further details regarding PROs conducted in previous studies on benralizumab treatment).

*Study duration*

The primary aim of this study is to understand the short-term impact of benralizumab on airway dynamics and structure that would reflect as improvements in lung function and PRO measurements, that of which were well established in previous trials studying the effects of benralizumab treatment. These improvements in lung function and PRO measurements were also confirmed in real-world evidence studies and seen in clinical practice.

The duration of this study is based on previous severe eosinophilic asthma imaging-based studies that have shown a rapid response on VDP and some PROs, such as CCI CCI at 28-days post-benralizumab, with changes detected as early as 14 days, and pronounced effects on patients with SEA and mucus plugs (McIntosh et al., 2020; McIntosh et al., 2021; Oguma et al., 2021) following treatment with benralizumab every 4 weeks.

Based on the observations from the imaging studies, further analyses were conducted on the results from the phase 3 SIROCCO and CALIMA studies on a subgroup of participants with a similar baseline profile for age, baseline eosinophilic levels, ICS dose and pre-BD FVC, to those who will be included in the current study. The results show improvements in change from baseline in $FEV_1$ as early as week 8 following treatment with benralizumab 30 mg every 4 weeks compared with the placebo arm (data on file). These observations provide support for assessing outcomes in patients treated with benralizumab for a shorter duration, while ongoing trials like the CHINOOK study with a study duration of one year, will take measurements as early as 8 weeks and will be repeated at week 48.

A 13 (± 1) week study duration was selected for this study to evaluate outcomes under treatment based on the above. Further, it is also to ensure the evaluation occurs at the middle time point between the third and fourth dose of benralizumab 30 mg to increase the likelihood that participants have optimal serum concentrations during evaluation of the final measurements for the study.

*Patient-reported Outcomes (PROs)*

The benefits shown on other PROs at 28-days post-benralizumab (McIntosh et al., 2020; McIntosh et al., 2021; Oguma et al., 2021) also suggest the possible value of exploring the relationship with CCI CCI - a new tool, and potentially understand how it could correlate with the airway dynamic measurements. The inclusion of other fit-for-purpose PROs CCI

Change in CCI following benralizumab treatment was studied in phase 3 asthma exacerbation studies, SIROCCO (Bleecker et al., 2016) and CALIMA (FitzGerald et al., 2016), the OCS reduction study, ZONDA (Nair et al., 2017), long-term extension trial, BORA (Fitzgerald et al., 2019), and the phase 3b ANDHI study in patients with severe uncontrolled

asthma on standard of care (Harrison et al., 2021), and will also be studied in ongoing trials like CHINOOK (NCT03953300, ClinicalTrials.Gov). In SIROCCO and CALIMA, improvements in ACQ-6 score were reported following benralizumab treatment in participants treated every 4 weeks and every 8 weeks (Bleecker et al., 2016; FitzGerald et al., 2016; Fitzgerald et al., 2019). Benralizumab also improved ACQ-6 scores at week 24 versus placebo, with differences observed within weeks 1 to 4 of treatment in the ANDHI study – notably, the first three doses of benralizumab were given 4 weeks apart followed by dosing every 8 weeks (Harrison et al., 2021). Changes in CCI score was also studied in the ANDHI trial where 24 weeks of benralizumab treatment provided clinically meaningful and statistically significant improvements in CCI total score versus placebo (Harrison et al., 2021). The inclusion of CCI will also thus allow the outcomes from the current study to be put into context from previous PRO-related findings following benralizumab treatment, as well as explore content similarities and differences between CCI

*Age Selection*

Only participants ≥ 18 years old will be eligible to participate in the study as there is currently no data are available for children aged 6 to 11 years old with the treatment of benralizumab, and while data is available in adolescents aged 12 to less than 18 years old permitting use of benralizumab in this patient group by the US FDA in the United States, the EMA made no recommendation on a posology. The current study will enroll participants from the US and EU. Therefore, an older age limit has been placed to allow only participants ≥ 18 years old.

There are no overall differences in safety or effectiveness observed between geriatric patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, participants older than 70 years will not be allowed to participate.

## 4.3 Justification for Dose

For this drug-device study intervention, the term “dose” refers to the amount of benralizumab administered via its device to the participant at weeks 0 (Visit 1), 4 (Visit 2), and 8 (Visit 3) respectively. In this study, participants will receive a total of three subcutaneously (SC) applied doses of 30 mg benralizumab.

The 30 mg Q4W (for the first 3 doses) then Q8W (for subsequent doses) dosing regimen is currently approved for treatment of severe asthmatics with an eosinophilic phenotype by the US FDA and EMA. Therefore, based on the duration of this study ie, 13 weeks, a 30 mg dose of benralizumab will be administered SC Q4W for the 3 doses at weeks 0, 4 and 8.

## 4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of

the study including all procedures listed in the Schedule of Activities (SoA) at week 13 (± 1 week).

The end of the study is defined as the date of the last expected visit/contact of the last participant undergoing the study.

# 5 STUDY POPULATION

This mechanistic study will investigate the short-term benefits of sustained depletion of airway eosinophils by benralizumab on airway dynamics and mucus plugs in participants with severe eosinophilic asthma. The inclusion and exclusion criteria listed below were defined to ensure that the patient population of interest will be enrolled, reflecting similar criteria as the SIROCCO and CALIMA studies, and consistent with the population where benralizumab is approved by the US FDA.

In addition, a review of the results from previous phase 3 and 4 trials was performed to enable participants in the current study to reflect the more severe patient population and those who are more prone to mucus plugging, therefore poorer outcomes, and would benefit most from benralizumab treatment. Specific criteria (e.g., FVC and ACQ-6) were selected through this review.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, are not permitted.

## 5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply at Visit 0 (V0; screening visit):

**Age**

1 Participants must be 18 to 70 years of age inclusive.

**Type of Participant and Disease Characteristics**

2 Participants who are diagnosed with asthma according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) clinical guidelines (2014) (Chung et al., 2014), with documented reversibility post-bronchodilator (after 2 to 4 puffs of albuterol [in the US] or salbutamol [in other countries] – see Section 8.1.2), either historical (medical records) or at Visit 0 (V0).

- Reversibility is defined as an increment of ≥ 12% and ≥ 200 mL in $FEV_1$ and/or FVC compared with baseline during a single testing session in accordance with the 2005 ERS/ATS guidelines (Pellegrino et al., 2005).

3 Participants who have documented treatment with ICS and LABA for ≥ 3 months prior to Visit 0 (V0), with or without oral corticosteroids and additional asthma controllers.

- ICS and LABA can be components of a fixed dose combination product or given as separate inhalers.

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

4 Participants who have documented peripheral blood eosinophil count ≥ 300 cells/μL at Visit 0 (V0), or if OCS-dependent, a documented peripheral blood eosinophil count ≥ 150 cells/μL at Visit 0 (V0). For study sites in Belgium, all participants, irrespective of OCS-dependency must have a blood eosinophil count ≥ 300 cells/μL at Visit 0 (V0):

- OCS-dependent asthma is defined as long-term OCS therapy (prednisone ≥ 5 mg/day for ≥ 3 continuous months directly preceding Visit 0 (V0) documented on medical records;
- Are required to receive stable OCS dosage for ≥ 4 weeks before Visit 0 (V0).
- Alternate OCS dosing (e.g., every other day), other dosing frequencies, and OCS therapy other than prednisone/prednisolone are allowed provided the average daily dose is equivalent to ≥ 5 mg of prednisone.
- Should remain on stable OCS dosing for the duration of the study.

5 Participants who have had a minimum of 2 exacerbations in the last 12 months prior to Visit 0.

- Last exacerbation is required to be no less than 6 weeks before Visit 0 (V0)
- Asthma exacerbation is defined by a worsening of asthma requiring:
  - Use of systemic corticosteroids (or a temporary increase in a stable oral corticosteroid background dose) for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids
  - An emergency room/urgent care visit (defined as evaluation and treatment for < 24 hours in emergency room [ER] or urgent care center) due to asthma that required systemic corticosteroids (as per above)
  - An inpatient hospitalization due to asthma (defined as an admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours)

6 Participants who have pre-bronchodilator $FEV_1/FVC \leq 70\%$ at Visit 0 (V0).

7 Participants who have pre-bronchodilator $FEV_1 < 80\%$ of predicted at Visit 0 (V0).

8 Participants who have ACQ-6 score ≥ 1.5 at Visit 0 (V0).

9 Participants who are non-smokers or ex-smokers who have stopped smoking at least 12 month(s) prior to Visit 0 (V0) and have a smoking history of < 10 pack years at Visit 0 (V0).

- Participants who use e-cigarettes or smoke marijuana will be excluded from the study.

10 Participants who have stable asthma regimen apart from the use of rescue medication including the use of any other asthma medication for at least 3 months prior to Visit 0 (V0).

11 Participants who are medically able to tolerate permitted medications without significant adjustment of dosage, formulation or dosing interval for the duration of the study, and is deemed able to withhold therapy for the specified time interval by the Investigator prior to Visit 0, 1 and 4. This includes the ability to withhold all inhaled [redacted] for at least 6 hours, all short-acting muscarinic antagonists (SAMAs) and all [redacted]/SAMA combinations for at least 12 hours prior to lung function assessments and/or high-resolution CT scans on Visit 0, 1 and 4.

12 Participants who can perform acceptable and repeatable spirometry according to the ATS/ERS 2019 criteria (Graham et al., 2019) and/or protocol-defined criteria.

- Note: If the participant cannot meet this criterion, retest is permitted and will be considered a rescreen. See Section 5.4 for further details.

13 Participants who can withhold asthma maintenance medication for at least 12 hours prior to Visit 0, 1 and 4 where spirometry and/or CT scan procedures will be performed, except for once-a-day dosage where 24 hours will be required.

14 Participants who are free of any concomitant conditions or treatments (including use of oral or ophthalmic beta blockers and/or immune suppressive medications), in the opinion of the investigator, that could interfere with study conduct, influence the interpretation of study observations/results, or put the patient at increased risk during the study.

15 Participants must be able to understand and complete the protocol requirements, PRO [redacted] and protocol-stated restrictions and be able to adhere to regularly scheduled asthma medication as judged by the investigator.

**Sex and Gender**

16 Persons of any sex and gender

17 Female participants:

Female participants who cannot bear children as evidenced by:

- 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 amenorrhoeic 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 amenorrhoeic 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 women of childbearing potential (WOCBP)

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

- If the above criteria are not met, the participant should be regarded as having childbearing potential.

  Persons capable of becoming pregnant and both of the following conditions are met:

  - Have a negative pregnancy test (urine/serum as per current clinical study protocol [CSP] template) prior to administration of the investigational product (IP) and high-resolution CT scan and

  - Must agree to use a highly effective method of birth control (confirmed by the investigator – and consistent with local regulations regarding the methods of contraception for those participating in clinical studies) from randomization throughout the study duration and within 12 weeks after last dose of IP. Highly effective methods (those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation- oral, intravaginal, or transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation- oral, injectable, or implantable
    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Sexual abstinence, ie, 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

**Informed Consent**

18 Provision of signed informed consent as described in Appendix B which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

## 5.2 Exclusion Criteria

### 5.2.1 Assessments at Visit 0 (screening visit)

Participants are excluded from the study if any of the following criteria apply at Visit 0 (V0; screening visit):

**Medical Conditions**

1 Participants who are unstable or who experienced an exacerbation/infection in the 6 weeks before Visit 0 (V0).

- Note: Participants may be rescreened after resolution of the exacerbation/infection and at least 4 weeks after the last dose of any medication to treat the exacerbation/infection (or return to baseline dose of OCS for those on chronic OCS).

2 Participants with acute upper or lower airway infection in the 6 weeks before Visit 0 (V0).

3 Participants with current malignancy or history of malignancy (Except for: Participants who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible, provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent, and assent when applicable, was obtained.)

- Participants who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to Visit 0 (V0), and assent when applicable, was obtained.

4 Participants diagnosed with clinically important pulmonary disease other than asthma (including but not limited to active lung infection, COPD, presence of emphysema on previous CT imaging, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, active tuberculosis, and primary ciliary dyskinesia) or participants who have ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (e.g. allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome and hypereosinophilic syndrome).

5 As judged by the investigator, any evidence or history of other clinically significant disease or abnormality such as congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, stroke, glaucoma or cardiac dysrhythmia, untreated moderate to severe sleep apnea, malignancy (excluding basal cell

carcinoma), a helminth parasitic infection diagnosed within 24 weeks prior to Visit 0 (V0) which has not been treated with or has failed to respond to standard of care therapy. In addition, historical or current evidence of significant hematologic, hepatic, neurologic, psychiatric, renal, pulmonary, or other diseases which in the investigator's opinion would put the participant at risk through study participation, or would affect the study analyses if the disease exacerbated during the study.

6 Participants with current active liver disease:

- Chronic stable hepatitis B and C (including positive testing for hepatitis B surface antigen [HBsAg] or hepatitis C antibody), or other stable chronic liver disease are acceptable if subject otherwise meets eligibility criteria. Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice, or cirrhosis.
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥ 3 times the upper limit of normal (ULN), confirmed by repeated testing during screening period. Transient increase of AST/ALT level that resolves by the time of study entry is acceptable if in the investigator’s opinion the subject does not have active liver disease and meets other eligibility criteria.

7 Participants known to have tested positive for human immunodeficiency virus.

8 Participants with inability to discontinue prohibited medications during Visit 0 (V0) and treatment periods.

9 Participants with documented or suspected viral or bacterial, ongoing infections, or illness within 4 weeks prior to the Visit 0 (V0).

10 Current evidence or known history of alcohol or substance abuse that could be of clinical significance as determined by the investigator as any conditions associated with poor compliance.

11 Participants who are scheduled to be admitted to hospital or undergo inpatient surgery during the study.

**Prior/Concomitant Therapy**

12 Receipt of any biologic products for asthma (e.g., omalizumab, mepolizumab) within 4 months or 5 half-lives prior to Visit 0 (V0), whichever is longer. Participants who received Fasenra® any time prior to Visit 0 (V0) will also be excluded.

13 Receipt of live acting live attenuated vaccines 30 days prior to Visit 0 (V0).

14 History or current use of chronic (ie, > 4 weeks) immunosuppressive medication (including but not limited to: methotrexate, troleandomycin, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid, chronic systemic corticosteroid including OCS [for conditions other than asthma], or any experimental anti-inflammatory therapy) within 3 months prior to Visit 0 (V0).

- Receipt of immunoglobulin or blood products within 30 days prior to Visit 0 (V0).
- Receipt of live attenuated vaccines 30 days prior to Visit 0 (V0). Receipt of inactive/killed vaccinations (e.g., inactive influenza) is allowed provided they are not administered within 1 week before/after any IP administration.
- Change to allergen immunotherapy or new allergen immunotherapy within 30 days prior to Visit 0 (V0) and anticipated changes in immunotherapy during the study.

15 History of lung volume reduction surgery, lung resection, thermal bronchoplasty at any time before visit 0 (V0) or on active phase of pulmonary rehabilitation.

**Prior/Concurrent Clinical Study Experience**

16 Participation in another clinical study with an Investigational biologic product within 4 months or 5 half-lives prior to Visit 0 (V0), whichever is longer.

17 Participation in another clinical study with an Investigational nonbiologic administered within 30 days or 5 half-lives prior to Visit 0 (V0), whichever is longer.

18 Participants with a known hypersensitivity to benralizumab or any of the excipients of the product.

19 Participants with history of anaphylaxis to any biologic therapy or vaccine.

**Diagnostic Assessments**

20 Participants with any clinically significant abnormal findings in physical examination, vital signs, hematology or clinical chemistry during screening/run-in period, which in the opinion of the Investigator, may put the participant at risk because of his/her participation in the study, or may influence the results of the study, or the participant's ability to complete entire duration of the study.

**Other Exclusions**

21 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site and their immediate relative(s)).

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

23 Previous enrolment in the present study unless participant fulfils on criteria for rescreening (see Section 5.4).

24 For women only - currently pregnant, lactating or breastfeeding, or plans to become pregnant during the study period or for 30 days after the participant's last study-related visit (for eligible participants only, if applicable). Eligible female participants unwilling to employ appropriate contraceptive measures to ensure that pregnancy will not occur during

the study will be excluded. Any participants becoming pregnant during the study will be withdrawn from the study.

25 Judgement by the investigator that there are physical factors (e.g., infirmity, disability, or geographic location) that the Investigator determines would likely limit compliance with the study protocol or study visits.

26 Participants who are current smokers or ex-smokers who have stopped smoking within 12 month(s) prior to Visit 0 (V0) and/or have a smoking history of ≥ 10 pack years, or who use e-cigarettes or smoke marijuana will be excluded from the study.

27 COVID-19:

Participants with:

- Positive COVID-19 test (as per prevailing local guidelines for COVID-19 testing at the time of the COVID-19 test) at Visit 0 (V0).
  - Participants that are asymptomatic and tested positive at Visit 0 (V0) may be rescreened after a minimum of 2 weeks at the investigator's discretion.
- COVID-19 disease within 6 weeks before Visit 0 (V0).
  - Participants may be rescreened after a minimum of 6 weeks at the investigator's discretion only if they had mild or moderate COVID-19 disease.
- History of severe COVID-19 disease at any time, defined by the need for Intensive Care Unit stay or Mechanical Ventilation (invasive or non-invasive) or per investigator's judgement.
  - Rescreening is not permitted for participants who had severe COVID-19 disease.

### 5.2.2 Re-assessment at Visit 1

Participants should have the following criteria reviewed at Visit 1 (V1), before any baseline assessment is performed.

1 Stable asthma regimen apart from the use of rescue medication including the use of any other asthma medication for ≥ 3 months prior to Visit 1 (V1).

2 OCS-dependent participants (as defined per the inclusion criterion #4) are required to receive stable OCS dosage for ≥ 4 weeks before Visit 1 (V1).

3 Last exacerbation (as defined per the inclusion criterion #5) is required to be no less than 6 weeks before Visit 1 (V1).

Visit 1 (V1) may be rescheduled 1 time per Section 5.5 in cases where baseline assessments cannot be performed because participants did not fulfil any of the above criteria at Visit (V1), (see Section 5.5).

## 5.3 Lifestyle Considerations

1) Persons who are having sexual relationships in which they may become pregnant must use highly effective contraceptive methods throughout the study and at least for 12 weeks after last dose of study intervention, as stated in inclusion criterion #17, Section 5.1.
2) Participants must abstain from donating blood, plasma, or platelets from the time of informed consent or assent (if applicable) and for 12 weeks after last dose of study intervention.
3) Live attenuated vaccines
   (a) Receipt of live attenuated vaccines is disallowed 30 days prior to first dose of study intervention, during study intervention administration, and for 12 weeks after last dose of study intervention.
4) Inactive/killed vaccinations (e.g., inactive influenza)
   (a) Not recommended within the 7 days before or within 7 days after any study intervention dosing study visit.
5) Any investigational product
   (a) Investigational biologic product not allowed within 4 months or 5 half-lives prior to Visit 0 (V0), whichever is longer.
   (b) Investigational product administered within 30 days or 5 half-lives prior to Visit 0 (V0) is not allowed, whichever is longer.

### 5.3.1 Meals and Dietary Restrictions

1) Participants should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the center.

### 5.3.2 Alcohol, Tobacco, E-cigarettes and Marijuana

1) Alcohol or drug abuse (including smoking of marijuana) is prohibited prior to screening and throughout the conduct of the study.
2) Use of tobacco products (including nicotine patches, marijuana and e-cigarettes) is prohibited within 12 months prior to screening and throughout the conduct of the study (see Section 5.2.1, criterion #26, for specific criteria for ex-smokers).

### 5.3.3 Activity

1) Blood pressure (BP) and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones). Respiratory rate will be obtained after participant has been resting for at least 5 minutes.

2) Participants should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the center.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned in the study, unless otherwise specified by the protocol. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes visit date (VISIT) demography (DM), informed consent (CONSENT), screen failure details, eligibility criteria (IE), and any serious adverse event (SAE).

For participants considered as "screen failure" due to one or more of the criteria listed below, there is an opportunity to be rescreened once. If a second rescreening is required, these cases should be discussed with the AstraZeneca Study Physician and documented in the investigator study file (ISF). Rescreened participants should be assigned a new participant number.

- Inability to perform acceptable and repeatable spirometry according to the ATS/ERS 2019 criteria (Graham et al., 2019) and/or protocol-defined criteria
  - If the participant cannot meet the criterion, the test may be rescheduled 1 week/7 days later and participants may be rescreened at the date of the retest.
- Participants who are unstable, who developed an exacerbation/infection in the 6 weeks before Visit 0 (V0).
  - Participants may be rescreened after resolution of the exacerbation/infection and at least 4 weeks after the last dose of any medication to treat the exacerbation/infection.
- Participants with positive COVID-19 test at Visit 0 (V0) - as per prevailing local guidelines for COVID-19 testing
  - Participants that tested positive at Visit 0 (V0) may be rescreened after a minimum of 2 weeks if they had an asymptomatic COVID-19 infection.
  - Participants that tested positive at Visit 0 (V0) and presented with mild or moderate COVID-19 disease may be rescreened after a minimum of 6 weeks at the investigator's discretion (see Section 5.2.1, criterion #27).
- Reason for screen failure was transient (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits, etc.), or due to a civil crisis, natural disaster, or public health crisis.
  - Note that these cases should be discussed with the AstraZeneca Study Physician and documented in the ISF. Re-screening of a participant for any other reason may be allowed only upon approval of the AstraZeneca Study Physician.

Any rescreened participant will be re-enrolled and assigned a new enrolment number after signing a new ICF and after all assessments during the screening visit (V0) have been performed as listed in Table 1. A documented approval for re-screening for any other reasons not mentioned above or a for a second rescreening should be filed in the ISF.

## 5.5 Visit rescheduling

Visits may be rescheduled within the visit window established in the SoA (Table 1). If a visit needs to be rescheduled outside the pre-specified visit window and the participant did not meet any of the conditions specified in Sections 5.5.1, 5.5.2 and 5.5.3 below, the case should be discussed with the AstraZeneca Study Physician and documented in the ISF. Extension of the run-in period for a participant for any other reason may only be allowed upon approval of the AstraZeneca Study Physician.

### 5.5.1 Participants who do not meet criteria at Visit 1

Participants who do not meet the criteria at Visit 1 (Section 5.2.2) are not allowed to proceed with any study baseline assessments and Visit 1 should be rescheduled to a timepoint where participants can fulfil these criteria. For acute asthma exacerbation or acute upper or lower respiratory tract infection, refer to Section 8.3.

### 5.5.2 Participants who are unable to come for Visit 1

Visit 1 should be rescheduled as soon as possible, or when considered safe as judged by the Investigator in the following transient situations/reasons:

- Including, but not limited to, study-supplied equipment failure, unforeseen personal events that mandate missing Visit 1, etc.
- Civil crisis, natural disaster, or public health crisis.

### 5.5.3 Visits 2, 3 and 4, and Follow-up

In general, Visits 2, 3, and 4, and the follow-up may be re-scheduled within the respective visit windows established in the SoA (Table 1). Rescheduling of visits beyond the visit window indicated in the SoA (Table 1) should be an exception and the reason should be recorded in the ISF.

### 5.5.4 COVID-19 positive test

COVID-19 testing should follow prevailing local guidelines at the time of the COVID-19 testing procedure and participants are considered as having positive COVID-19 test when they fulfill the criteria defined as per aforementioned local guidelines.

Participants who have a positive COVID-19 test and are asymptomatic (or have mild disease without lower respiratory tract symptoms – per investigator's judgement) are allowed to have the visits rescheduled as follows:

- Participants who have a positive COVID-19 test immediately before Visit 1 *AND* are asymptomatic: delay Visit 1 up to 14 days (in accordance with local guidelines for quarantine and re-testing procedure) from the date when the test was performed.
- Participants who have a positive COVID-19 test immediately before Visit 2 or Visit 3 *AND* are asymptomatic should receive the study intervention drug within the allowed visit window established in the SOA (Table 1).
- Participants who have a positive COVID-19 test immediately before Visit 4 *AND* are asymptomatic: delay Visit 4 up to 14 days (in accordance with local guidelines for quarantine and re-testing procedure) from the date when the test was performed.

Participants with any moderate or severe COVID-19 disease, or COVID-19 disease with lower respiratory tract symptoms, irrespective of severity, at any time during the study period shall be discontinued (see Section 7.1).

In case the reason for postponing is an acute exacerbation or respiratory tract infection, refer to Section 8.3 for instructions.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

## 6.1 Study Intervention(s) Administered

### 6.1.1 Investigational Products

| | |
|---|---|
| **Arm name** | Benralizumab |
| **Intervention name** | Benralizumab (Fasenra) |
| **Type** | Combination Product |
| **Dose formulation** | Single-use pre-filled syringe (injection)<br>One mL solution in a single-use pre-filled syringe made from type I glass with a staked 29-gauge ½-inch (12.7 mm) stainless steel needle, rigid needle shield, and Fluorotec-coated plunger stopper in a passive safety device. |
| **Unit dose strength(s)** | 30 mg |
| **Dosage level(s)** | 3 doses, once every 4 weeks (at baseline [V1], week 4 [V2] and week 8 [V3]) |
| **Route of administration** | Subcutaneous |
| **Use** | Other (Phase 4) - Treatment of severe asthma per current approved USPI and EU SmPC/European Public Assessment Report (EPAR) |
| **IMP and NIMP** | IMP |
| **Sourcing** | Provided centrally by the sponsor; manufactured by AstraZeneca AB |
| **Packaging and labelling** | Study Intervention will be provided in pre-filled syringe.<br>Each pre-filled syringe will be labelled in<br>accordance with Good Manufacturing Practice (GMP) Annex 13 and as required per country regulatory requirement. Label text will be translated into local languages as required |
| **[Current/former name(s) or alias(es)]** | MEDI-563 |

### 6.1.2 Medical Devices

#### 6.1.2.1 Benralizumab pre-filled syringe

1) The AstraZeneca manufactured medical devices (or medical devices manufactured for AstraZeneca by a third party) provided for use in this study are,
    - Syringe prefilled with benralizumab (Status, US FDA and EMA approved)

2) Instructions for medical device use are provided in Product Full Prescribing Information / Product Package Leaflet, Product Instructions for Use in the local language (for home administration) and/or patient information leaflet.
3) All medical device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.10) and appropriately managed by the sponsor.

#### 6.1.2.2 Respiratory Gating Device

1) The Geratherm Respiratory manufactured medical devices (or medical devices manufactured for Geratherm Respiratory by a third party) provided for use in this study are,
    - Spirotik (Status, CE-marked [according to Medical Device directive])

      This is a portable spirometer that comes with disposable mouth pieces and nose clips, and operates through a software, Blue Cherry (Geratherm Respiratory), using a laptop. This device will be used to monitor participants' breathing during the CT scan procedure to ensure CT scans are taken at the correct breathing level.
2) Instructions for medical device use are provided in a separate CT scan manual and e-course materials provided by a central vendor.
3) All medical device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.10) and appropriately managed by the sponsor.

## 6.2 Preparation/Handling/Storage/Accountability

1) The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2) Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
3) The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4) Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

The IP will be administered at the study site on Visit 1, 2 and 3. IP will be supplied to the site in a kit with a single-use pre-filled syringe of benralizumab. Dosing should be performed following the completion of all visit assessments for Visit 1, 2 and 3.

All shipments of IP include a data logger which will allow the Investigator or designee to confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before the use of the study treatment. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply the study treatment.

Only authorized site staff may administer the study treatment.

**Before investigational product administration**

Prior to each IP administration:

1) The Investigator/authorized delegate will assess the injection site as per the standards of medical care.
2) For WOCBP, a urine pregnancy test will be performed; IP will be administered only if the result of the test is negative.

**Investigational product administration**

The IP will be administered by the Investigator/authorized delegate. Investigational product at a dose of 30 mg should be administered SC using the pre-filled syringe into the upper arm, thighs, or the abdomen (see Figure 2). It is suggested that the site of injection is rotated such that the participant receives IP at a different anatomical site at each treatment visit. Investigational product should not be administered into areas where the skin is tender, bruised, erythematous, infected or hardened, or where there is an open graze.

**Figure 2 Suggested schema of injection sites**

Further details on IP administration are described in the IP Handling Instruction provided to study sites. Investigational product administration must be carried out in line with the Instruction.

**After investigational product administration**

Participants should be observed according to clinical practice after administration of IP for the appearance of any acute drug reactions.

**Conditions requiring investigational product administration rescheduling**

Administration of the IP may only be rescheduled if:

1) Rescheduled date of IP administration falls within the visit window indicated in the SoA.
    - Note: Dose interruptions requiring rescheduling of IP administration outside the visit window indicated in the SoA are not permitted (see Section 7.1.1 for further details).
2) Participant needs to reschedule Visit 1 per Section 5.5.1 and 5.5.2 (see Section 5.5 for further details).

## 6.3 Measures to Minimize Bias: Randomization and Blinding

The current study is an open-label study with no blinding at site level.

## 6.4 Study Intervention Compliance

The administration of all study treatments should be recorded in the appropriate section of the electronic Case Report Form (eCRF). The study treatment provided for this study will be used only as directed in this CSP. The study treatment will be administered at the study site on treatment visits (Visit 1, 2 and 3) as specified in the SoA (Table 1). Participants who cannot

receive the first study treatment at Visit 1 as described in Section 5.5.1 and 5.5.2 may be rescheduled (see Section 5.5 for further information). The second and third study treatment must be administered within the visit window as specified in the SoA (Table 1). Any change from the dosing schedule (dose interruptions or dose discontinuations) should be recorded in the eCRF. It should be noted that dose modifications are prohibited and will be considered as a discontinuation of study intervention.

The participants will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine the pre-filled syringe to ensure that the study intervention was administered completely.

Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

## 6.5 Concomitant Therapy

The participants' ICS or OCS and additional asthma maintenance medication at enrolment will remain unchanged during the run-in and treatment period. Maintenance and rescue asthma medications are not regarded as an IP and will not be provided/reimbursed by AstraZeneca.

To satisfy inclusion criterion #3, a history of continuous treatment with high-dose ICS and LABA for ≥ 3 months prior to Visit 0 (V0), with or without oral corticosteroids and additional asthma controllers should be documented in source and recorded in the eCRF at Visit 0 (V0). If the participant is taking ICS plus LABA, the ICS and LABA can be parts of a combination product or given by separate inhalers. The ICS dose must be > 500 µg/day fluticasone propionate dry powder formulation or equivalent daily. For ICS/LABA combination preparations, the highest approved maintenance dose in the local country will meet this ICS criterion.

In order to satisfy inclusion criterion #4, a history of OCS therapy (prednisone ≥ 5 mg/day for ≥ 3 continuous months directly preceding Visit 0 (V0) and stable OCS dosage for ≥ 4 weeks before Visit 0 (V0) should be documented in source and recorded in the eCRF at Visit 0 (V0). Alternate OCS dosing (e.g., every other day), other dosing frequencies, and OCS therapy other than prednisone/prednisolone are allowed provided the average daily dose is equivalent to ≥ 5 mg of prednisone. Participants should also remain on stable OCS dosing for the duration of the study.

In order to satisfy inclusion criterion #10, participants are required to remain on a stable

asthma treatment regimen apart from the use of rescue medication including the use of any other asthma medication for at least 3 months prior to Visit 0 (V0). The Investigator will record information on background therapy compliance during the study in the eCRF.

All medications taken in the 3 months prior to Visit 0 (V0) and throughout the study must be recorded in the eCRF along with the reason for treatment by the Investigator/authorized delegate at each visit, as specified in Table 1.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

Reason for use

- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

**Table 4 Restricted medicines**

| Medication/class of drug | Usage (including limits for duration permitted and special situations |
|---|---|
| Maintenance treatment with ICS and LABA (including ICS/LABA combinations) | No changes in either dose or regimen are allowed from screening visit (V0) and throughout the IP treatment.<br>Budesonide/Formoterol "MART" reliever therapy is allowed as rescue medication and its use as a rescue medication will be recorded in the eCRF.<br>Twice daily BDs should be withheld for at least 12 hours prior to Visit 0, 1 and 4 at the site.<br>Once daily BDs should be withheld for at least 24 hours prior to Visit 0, 1 and 4 at the site. |
| Maintenance treatment with LAMA (isolated or in combinations) | No changes in either dose or regimen are allowed from screening visit (V0) and throughout the IP treatment.<br>Twice daily LAMAs should be withheld for at least 12 hours prior to Visit 0, 1 and 4 at the site.<br>Once daily LAMAs should be withheld for at least 24 hours prior to Visit 0, 1 and 4 at the site. |
| CCI [redacted] | CCI [redacted].<br>CCI [redacted] |

| Medication/class of drug | Usage (including limits for duration permitted and special situations |
|---|---|
| Short-acting muscarinic antagonist (SAMA) | SAMA is allowed as rescue medication.<br>SAMA should be withheld for at least 12 hours prior to Visit 0, 1 and 4 at the site. |
| CCI /SAMA combinations | CCI /SAMA combination is allowed as rescue medication.<br>CCI /SAMA combination should be withheld for at least 12 hours prior to Visit 0, 1 and 4 at the site. |
| Additional maintenance controllers | Leukotriene receptor antagonists (LTRA) should be restricted for at least 24 hours prior to the scheduled spirometry test at Visit 0 (V0), and prior to scheduled Visit 1 and 4, at the site.<br>Twice daily theophyllines should be withheld for at least 12 hours prior to Visit 0, 1 and 4 at the site.<br>Once daily theophyllines should be withheld for at least 24 hours prior to Visit 0, 1 and 4 at the site. |
| Intranasal steroid | Intranasal steroid is allowed at the discretion of the Investigator. |
| Chronic immunosuppressive medication (including corticosteroids) or any experimental anti-inflammatory therapy | Not allowed within 3 months prior to Visit 0 (V0) as per exclusion criterion #14.<br>Chronic oral corticosteroids for asthma are allowed as per Section 5.1, inclusion criterion #3<br>Topical administration of immunosuppressive medication may be administered at the Investigator's discretion as clinically indicated. |
| Allergen immunotherapy | Allowed if on stable therapy for at least 30 days prior to Visit 0 (V0), with no anticipated change during the study.<br>The participant should not receive an allergen immunotherapy injection on the same day as the IP administration. |
| Inactive/killed vaccinations | Receipt is allowed provided they are not administered within 7 days before/after any IP administration. |

## Table 5 Prohibited medicines

| Prohibited medication/class of drug: | |
|---|---|
| Immunoglobulin or blood products | Use prohibited within 30 days prior to visit 0 (V0). Immunoglobulin is not allowed during the study except for treatment of an AE, as judged by the Investigator. |
| Marketed or investigational biologic (monoclonal or polyclonal antibody) | Use prohibited within 4 months or 5 half-lives (whichever is longer) prior to Visit 0 (V0), and during the study. |
| Live/attenuated vaccines | Use prohibited 30 days prior to Visit 0 (V0), during the treatment period, and for 12 weeks after the last dose of the IP. |
| Previously received benralizumab | Prohibited. |

| **Prohibited medication/class of drug:** | |
|---|---|
| Any other Investigational product | Use prohibited within 30 days or 5 half-lives (whichever is longer) prior to Visit 0 (V0) and during the study. |
| Oral or ophthalmic non-selective β-adrenergic antagonist | Use prohibited as per inclusion criterion #14 unless it does not interfere with study conduct, influence the interpretation of study observations/results, or put the participant at increased risk during the study. |
| Change to allergen immunotherapy or new allergen immunotherapy | Use prohibited within 30 days prior to visit 0 (V0). |
| Over-the-counter inhaled epinephrine | Use prohibited. |

Paracetamol/Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use any time during the study. Other concomitant medications not excluded based on inclusion criterion #14 and exclusion criteria #12 to #14, #16 and #17 are permitted for use any time during the study (see Section 5.1 and 5.2.1).

**Table 6 Other prohibited treatments**

| **Prohibited treatments** | |
|---|---|
| Lung volume reduction surgery | Prohibited |
| Lung resection | Prohibited |
| Thermal bronchoplasty | Prohibited |
| Pulmonary rehabilitation | Active phase of rehabilitation is prohibited prior to screening and through the study |

### 6.5.1 Rescue Medicine

The sponsor will not supply any rescue medication.

Rescue use of medications administered via nebulization is discouraged, except as urgent treatment during an asthma exacerbation. Occasions where medications are administered via nebulization will be recorded separately from metered dose inhaler inhalations.

The following rescue medications may be used:

- CCI
  - CCI
- Short-acting muscarinic antagonists (SAMAs)

  - Short-acting muscarinic antagonists (SAMAs) should be withheld for at least 12 hours prior to Visit 0, 1 and 4 at the site.
- CCI and SAMA combinations
  - CCI /SAMA combinations should be withheld for at least 12 hours prior to Visit 0, 1 and 4 at the site.
- Maintenance and reliever therapy (MART)
  - MART reliever therapy and the use of Budesonide/formoterol as a rescue medication are allowed at the Investigator's discretion. Total ICS dose of MART maintenance therapy and whether it is used as rescue medication will be recorded in the eCRF.
  - MART reliever therapy should be withheld for at least 12 hours prior to Visit 0, 1 and 4 at the site (Table 4).
- Oral corticosteroids (OCS)
  - OCS use for the treatment of asthma exacerbation is allowed for the duration of ≤ 4 weeks. Longer treatment with OCS should be discussed with the AZ Study Physician to decide on the participant's disposition. Please refer to Section 8.3.1 for further instructions on study procedures in case of acute asthma exacerbation or respiratory tract infection.

## 6.6 Dose Modification

This protocol does not permit dose modification (see Section 4.3). Dosing can only be discontinued due to an AE per the Investigator's clinical judgement or unforeseen circumstances (see Section 7.1).

Any change from the dosing schedule (dose interruptions or dose discontinuations) should be recorded in the eCRF.

## 6.7 Intervention After the End of the Study

The investigator will discuss the available treatment options with participants who complete the study or who withdraw early from the study. The sponsor will not provide benralizumab upon study completion or early study withdrawal.

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Procedures for E/D follow-up should be followed as specified in SoA and the participant will be withdrawn from the study.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

If a participant has no baseline assessments which are successfully performed (PROs, CT scan or Spirometry) then the participant must be withdrawn from the study. Procedures and study intervention should be discontinued.

See the SoA (Table 1) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

## 7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and, if he/she had completed the study procedures at Visit 1 and have had at least one dose of the study intervention, baseline measurements will also be evaluated.

If a participant discontinued study intervention, procedures for an Early Study Intervention Discontinuation (E/D) follow-up should be followed as described in the SoA. Refer to Table 1 for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed

Participants may be discontinued from IP in the following situations.

- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment (see Section 7.2).
- An AE that is considered to jeopardize the safety of a participant participating in the study as judged by the Investigator or AstraZeneca.
- Positive pregnancy test at any time during the study (see Section 8.4.8 Pregnancy), or breastfeeding.
- Severe non-compliance with the CSP.
- Development of any study-specific criteria for discontinuation, including:
  - An anaphylactic reaction to the IP,
  - A helminth parasitic infestation requiring hospitalization,
  - An asthma-related event

    - requiring hospitalization for more than 24h or intubation,
    - requiring OCS treatment after week 11 (see Section 8.3.1 for further details)
  - Any new or recurrent malignancy, except non-melanoma skin cancers,
- -19
  - Moderate or severe disease at any time during the study period.
  - Mild disease with lower respiratory tract symptoms at any time during the study period.
  - Mild disease without lower respiratory tract symptoms may continue in the study at the investigator's discretion and visits rescheduled per Section 5.5.4.
  - Asymptomatic patients with COVID-19 positive test should not be discontinued and visits rescheduled per Section 5.5.4.

For details relating to dose modifications, see Section 6.6.

### 7.1.1 Temporary Discontinuation

Dose interruption requiring rescheduling of IP administration outside the visit window indicated in the SoA (Table 1) should be an exception and the reason should be recorded in the eCRF. Dose delays longer than 10 days may only happen upon approval of the AstraZeneca Study Physician and at the discretion of the Study Physician, and if not authorized will be considered a discontinuation of study intervention. Procedures for E/D follow-up should be followed as specified in the SoA (Table 1). Study treatment may be temporarily discontinued for reasons such as the following:

- Adverse event
- Unforeseen circumstances resulting in delayed visit (ie, illness, or personal events)

## 7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an Early Study Intervention Discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that

need to be completed. Then the participant will discontinue the study intervention and be withdrawn from the study at that.

A participant who withdraws consent will always be asked about the reason(s) and the presence of any AE and history of asthma exacerbation. The Investigator will follow up participants as medically indicated. A withdrawal visit is essential to collect as much safety data, as possible for the participant as per E/D described in the SoA (Table 1).

If the participant 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 participant chooses to withdraw from the study and as a result discontinues from the study intervention, if possible, an E/D follow-up should be conducted, as shown in the SoA (see Section 7.2 for further details). It should be confirmed if he/she still agrees for existing samples to be used in line with the original consent.

If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation The investigator must document the decision on use of existing samples in the site study records and inform the Study Team.

## 7.3 Lost to Follow-up

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix C.

# 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.

The Investigator will ensure that data are recorded in the eCRFs. An electronic system will be used for data collection and query handling. The Investigator will also ensure the accuracy, completeness, legibility, 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 eCRFs. A copy of the completed eCRFs will be archived at the study site. In case of civil crisis, natural disaster, or public health crisis, additional data to assess the impact of such events will be collected.

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

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant'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 time frame defined in the SoA.

The average amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be approximately 30 mL (depending on the local laboratory sample processing procedure) and will not exceed 50 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1 Efficacy Assessments

### 8.1.1 Functional Respiratory Imaging (FRI)

Functional Respiratory Imaging (FRI) is a quantitative method to measure biological responses to therapeutic interventions through structural and functional parameters using high-resolution CT and computational fluid dynamics. All CT scanners used in this study must be at least a 64-slice scanner. For a helical scan, the scanner should be able to acquire at least 64 slices per rotation using a slice thickness of 0.625 mm or lower (collimation of

64 x 0.625 mm, 128 x 0.5 mm, 256 x 0.6 mm, etc.) using a tube voltage of 100kV. FRI analyses will be conducted by a central vendor who will provide further guidance on the CT scanner requirements, CT scan procedure and scanner-specific scanning protocol settings required for the current study in a separate manual and guidance document. Study team training will also be provided by the central vendor to all relevant study team members prior to study center activation. Clinical evaluation of CT scans should be done by the study team as per local practice, and any abnormality identified should be recorded as an AE in the eCRF.

#### 8.1.1.1 FRI parameters

*Image acquisition*

In this study, the FRI parameters will be obtained through first the acquisition of low dose, high-resolution computed tomography (CT) thorax scans of participants in the study using a low radiation scanning protocol installed on a study-allocated CT scanner before study initiation at the study center.

All participants in the study will undergo two high-resolution scans, one each at Total Lung Capacity (TLC) and Functional Residual Capacity (FRC) with gating, at both Visits 1 and 4 as specified in the SoA (Table 1). All CT scans will be conducted with respiratory gating using equipment (CE-marked) provided by the central vendor. All CT scan procedures should also be conducted before spirometry testing (see Section 8.1.2 for further details).

Participants should withhold their usual maintenance and rescue therapies **before Visit 1 and Visit 4** where CT procedures will be scheduled as below:

- CCI [redacted]
- Short-acting muscarinic antagonists (SAMAs) or CCI [redacted]/SAMA combinations should be withheld at least 12 hours prior to Visit 1 and Visit 4 at the site.
- Twice daily LABA-containing therapies should be withheld for at least 12 hours prior to Visit 1 and Visit 4 at the site.
- Once daily LABA-containing therapies should be withheld for at least 24 hours prior to Visit 1 and Visit 4 at the site.
- Once daily LAMA-containing therapies should be withheld for at least 24 hours prior to Visit 1 and Visit 4 at the site.
- Twice daily LAMA-containing therapies should be withheld for at least 12 hours prior to Visit 1 and Visit 4 at the site.

- LTRA should be restricted for at least 24 hours prior to Visit 1 and Visit 4 at the site.
- Twice daily theophyllines should be withheld for at least 12 hours prior to Visit 1 and Visit 4 at the site.
- Once daily theophyllines for at least 24 hours prior to Visit 1 and Visit 4 at the site.

*Image processing*

All high-resolution CT images should be de-identified before upload to the central vendor where they will be imported into Mimics, a commercial, Food and Drug Administration approved, medical image processing software package (Materialise, Leuven, Belgium, Food and Drug Administration, K073468; CE certificate, BE 05/1191 CE01). Trained FRI analysts will implement validated protocols and algorithms to convert the high-resolution CT images into patient specific, segmented, three-dimensional (3D) computer models of the lung lobes, the airway lumen and wall, and the vascular tree. These models will then be used for performing measurements of the following structural and functional FRI parameters and used for further evaluations of functional FRI parameters that utilize computational fluid dynamics (CFD).

The following are the relevant structural and functional FRI parameters:

1. Untrimmed total mucus volume at TLC (Primary)
2. Untrimmed total mucus plugs score at TLC (Secondary)
3. Untrimmed total air trapping at FRC (Secondary)
4. Trimmed distal airway wall volume (iVaww) at TLC (Secondary)
5. Trimmed distal specific airway volume (siVaw) at TLC (Secondary)
6. Trimmed distal specific airway volume (siVaw) at FRC (Secondary)
7. Untrimmed total lung volume (iVlung) at TLC (Secondary)
8. Untrimmed total lung volume (iVlung) at FRC (Secondary)
9. CCI [redacted]

The computational fluid dynamics (CFD) approach will also be used to model exposure to inhaled particles. Specifically, aerosol deposition using CFD simulates the particle flow and particle behavior of within the reconstructed lungs of participants as a function of the specific inhalation profile, geometry of the airways and the drug particle size. In this study, aerosol deposition will be simulated based on inhalation of a generic CCI [redacted]

CCI [redacted] inhaler using selected inhalation flow profiles. Specific particle mass median aerodynamic diameter (MMAD +/- geometric standard deviation) of the relevant drug will be taken from published literature or data on file and 3D computer-aided design (CAD) file of the CCI [redacted] inhaler device will be obtained to conduct the aerosol deposition simulation.

Deposition in the intrathoracic and peripheral airways will be measured using CCI [redacted] drug deposition ratio before and after benralizumab treatment using lung models from high-resolution CT scans at week 0 (baseline) and week 13 (± 5 days). Central airway will be defined as the trachea and all airways with diameter > 1–2 mm and reaching out to 7–10th generation of dichotomous branching, while the peripheral airways will be defined as airways with a diameter < 1–2 mm and > 10 generations of branching. As detailed in the above list of relevant structural and functional FRI parameters, FRI analyses on CT scans at baseline (Visit 1) and following benralizumab treatment (at Visit 4) will be conducted on untrimmed or trimmed airways. Untrimmed analyses will include all airway branches visible at each visit, while the trimmed analysis will only include airway branches visible across both visits 1 and 4. All FRI parameters will be assessed in the different zones of the respiratory system - right upper lobe (RUL), right middle lobe (RML), right lower lobe (RLL), left upper lobe (LUL) and left lower lobe (LLL), as well as into central and distal regions, the latter two regions only for FRI parameters related to the airways (siVaw, and iVaww). Specifically, all FRI parameters related to the airways (siVaw and iVaww) will be assessed from generations 1 to 10 and reported by different zones of the respiratory system and by central and distal regions. Additionally, airway wall volume (iVaww) will be at generations 3 and 4, based on assessments planned for similar ongoing studies.

#### 8.1.1.2 Mucus Plugging

As detailed in the previous section, untrimmed total mucus volume at TLC and untrimmed mucus plugs score at TLC are FRI parameters of interest in the study.

Mucus plugging will be assessed visually through diligent segmentation of the airways. Airways will be segmented from central airways to distal airways by means of a deep learning Convolutional Neural Network (CNN) model to the extent which the resolution of the scanner allows. After segmentation of the airways, a mucus plug will be identified as such if the plug prematurely blocks or ends the airway segmentation and presents with an open airway after the plug (full occlusion). The above approach to mucus plug assessment allows for multiple, sequential mucus plugs from central to distal areas in the airway tree to be detected and included for analysis. Each bronchopulmonary segment will be given a score that directly represents the number of mucus plugs within that segment. Therefore, mucus plugs will be counted per segmental airway branch, and the total number of mucus plugs will be presented on a segmental, lobar (RUL, RML, RLL, LUL and LLL), and total level, by summing up the scores over the specific zones mentioned.

The volume of the mucus plugs will also be determined on lobar (RUL, RUML, RLL, LUL and LLL) and presented on the total level, by summing up the mucus volumes over the specific zones mentioned.

Next, with the use of data presented from the mucus plugging assessment above, mucus plugs will also be scored with a scoring system similar to that by Dunican et al. with the Severe Asthma Research Program (SARP) (Dunican et al., 2018), based on bronchopulmonary segmental anatomy. Each bronchopulmonary segment will be given a score of 1 (mucus plug present) or 0 (mucus plug absent). The segment scores of each lobe will be summed to generate a total mucus score for both lungs, yielding a mucus score ranging from 0-20. Of note is the means of determining whether a particular segment contained a mucus plug will differ from that described in Dunican et al., 2018 in that airways will be segmented as described above. The presence or absence of mucus within a given CNN-segmented airway will be determined according to the method also described above.

### 8.1.2 Spirometry

Lung function measurements will be assessed as part of efficacy assessment and at screening (Section 5.1 and 5.2).

Participants will need to undergo pre- and/or post-bronchodilator (pre-BD and post-BD) spirometry tests for this study to fulfil the inclusion criteria. Pre-BD spirometry testing will be conducted during Visit 0, Visit 1 and Visit 4 in accordance with the SoA (Table 1). Post-BD spirometry with reversibility testing will be conducted during Visit 0 if participants do not have historical documented reversibility available in medical records. If participants are unable to perform acceptable and repeatable spirometry during screening, a retest is permitted (see Section 5.4).

Post-BD spirometry should be initiated at least 15 minutes after BD dosing and should ideally be completed within 1 hour after BD administration. If more than 1 hour has passed since the BD dosing, additional puffs can be administered at the discretion of the Investigator.

The BD will be administered as follows: after a gentle and complete exhalation, 4 inhalations of albuterol (US; 90 µg metered dose) or salbutamol (other countries; 100 µg metered dose) should be administered using a spacer device. In rare cases where a participant has an adverse or allergic reaction to albuterol/salbutamol, levalbuterol (45 µg metered dose, 4 inhalations) can be used (Sorkness et al., 2008). A nebulizer should not be used. A lower total dose (e.g., 2 inhalations instead of 4 and if required up to a maximum of 4 puffs) can be used if there is a concern about any effect on the participants heart rate, tremor or safety; the reason should be noted in the participant's medical record.

Lung function ($FEV_1$ and FVC) will be measured by spirometry using equipment available at the study site. The highest technically acceptable pre- and/or post-BD $FEV_1$ and FVC will be captured. Spirometry will be performed by the Investigator or authorized delegate according to the 2005 ERS/ATS guidelines (Pellegrino et al., 2005). The responsible delegate at the facility where spirometry is conducted by the study center will be responsible for assuring that the spirometer is properly calibrated, meets ATS/ERS recommendations, and that the study center personnel who will be performing the testing are properly certified.

Participants should note the following before spirometry testing:

1) Avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry test at the center.

2) Avoid eating a large meal or drinking alcohol or caffeine containing beverages for at least 2 hours prior to spirometry test at the center.

3) Withhold their usual maintenance and rescue therapies **before Visit 0, Visit 1 and Visit 4** where spirometry testing will be scheduled as below:

   - CCI ) should be withheld at least 6 hours prior to Visit 0, Visit 1 and Visit 4 at the site.
   - Short-acting muscarinic antagonists (SAMAs) or CCI /SAMA combinations should be withheld at least 12 hours prior to Visit 0, Visit 1 and Visit 4 at the site.
   - Twice daily LABA-containing therapies should be withheld for at least 12 hours prior to Visit 0, Visit 1 and Visit 4 at the site.
   - Once daily LABA-containing therapies should be withheld for at least 24 hours prior to Visit 0, Visit 1 and Visit 4 at the site.
   - Twice daily LAMA-containing therapies should be withheld for at least 12 hours prior to Visit 1 and Visit 4 at the site.
   - Once daily LAMA-containing therapies should be withheld for at least 24 hours prior to Visit 0, Visit 1 and Visit 4 at the site.
   - LTRA should be restricted for at least 24 hours prior to Visit 0, Visit 1 and Visit 4 at the site.
   - Twice daily theophyllines should be withheld for at least 12 hours prior to Visit 0, Visit 1 and Visit 4 at the site.
   - Once daily theophyllines for at least 24 hours prior to Visit 0, Visit 1 and Visit 4 at the site.

On Visit 1 and Visit 4, the spirometry test should always be performed after the participants undergo the CT scan procedure as the procedures conducted during spirometry may impact

the CT scans. If not feasible, there should be at least 30 min between the spirometry test and subsequent CT scan procedure.

### 8.1.3 CCI

CCI

CCI

CCI

.

### 8.1.4 CCI

CCI

CCI

CCI [redacted]

### 8.1.5 CCI [redacted]

CCI [redacted]

CCI [redacted] administration at Visit 1, and prior to the CT scan procedure and spirometry test at Visit 4.

## 8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

### 8.2.1 Physical Examinations

A brief physical examination will be performed and include, at a minimum, assessments of the lungs, chest, head, eyes, ears, nose and throat.

Physical examination will be performed at timepoints as specified in the SoA (Table 1).

Any evidence of clinically significant abnormalities identified during the physical examination at screening and during the study will be recorded in the eCRF. Clinically significant abnormalities identified during physical examinations during the study should also be reported per Section 8.4.5.

### 8.2.2 Vital Signs

Vital signs (blood pressure and pulse) will be performed at timelines as specified in the SoA (Table 1).

Vitals signs will be measured during screening, at unscheduled visits and during an early

discontinuation visit. As per standard of care, vital signs may also be taken before blood draws, CT scan procedures, IP administration, and, prior to usual asthma maintenance medication Blood pressure and pulse measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is unavailable. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Any clinically significant abnormalities will be recorded in the eCRF and reported per Section 8.4.5.

### 8.2.3 Electrocardiogram

An electrocardiogram (ECG) will be performed at screening to access eligibility for the study as specified in the SoA (Table 1).

A12-lead ECG will be taken in supine position at screening (Visit 0), prior to blood draw, spirometry, and BD administration if applicable, at a local facility.

The Investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. The Investigator's interpretation should be noted on the printout and recorded in the eCRF. A copy of the ECG will be produced and kept in case of further need for re-evaluation.

Any clinically significant abnormalities will be reported per Section 8.4.5.

### 8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry and hematology will be taken at the visits indicated in the SoA (Table 1).

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units and reference ranges as specified in eCRF completion instructions) will be recorded on the appropriate eCRF.

Clinical chemistry and hematology will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

**Table 7 Laboratory Safety Variables**

| Haematology (whole blood) | Clinical Chemistry (serum or plasma) |
|---|---|

| | |
|---|---|
| Hemoglobin (Hb) | Alkaline phosphatase (ALP) |
| Leukocyte count | Alanine transaminase (ALT) |
| Leukocyte differential count (absolute count; including eosinophil absolute count) | Aspartate transaminase (AST) |
| Platelet count | Bilirubin, total |
| | Creatinine |
| | Glucose |
| | Potassium |
| | Sodium |

**NB.** In case a participant shows an AST **or** ALT ≥ 3 ×ULN at screening, participant will be excluded from the study.

#### 8.2.4.1 Pregnancy test

The following tests are applicable to female participants only, and will be conducted in accordance with the SoA (Table 1).

1) Serum β-human chorionic gonadotropin (β-HCG) – the test will be mandatory at screening for WOCBP. Testing will be conducted at a local laboratory at or near to the investigator site.
2) FSH – the test performed at screening only, for female participants to confirm postmenopausal status in women < 50 years who have been amenorrheic for > 12 months. Testing will be conducted at a local laboratory at or near to the investigator site.
3) Urine HCG – the test will be performed at the study site for WOCBP at Visits 1, 2, 3 and 4 using a dipstick. A negative urinary pregnancy test is required for WOCBP prior to study entry, CT scan procedure and administration of IP. A positive urine test result must be confirmed with serum β-HCG and if necessary, the visit can be rescheduled according to the SoA (Table 1).

Results from the tests should be recorded in the eCRF. Participants will be immediately discontinued from all study procedures and administration of IP following a positive urine pregnancy test and will be withdrawn from the study following confirmation with serum pregnancy test (see Section 7.1 and 8.4.8). Procedures for E/D follow-up should be followed as indicated in the SoA (Table 1).

### 8.2.5 COVID-19 Testing

Each investigator site shall follow prevailing local guidelines for COVID-19 testing before any visits or procedures.

If a participant presents with a positive COVID-19 test result, visits are permitted to be rescheduled per guidance provided in Section 5.5.4.

Participants with a positive COVID-19 test result and symptomatic disease should have their situation assessed and either discontinued per section 7.1 or have the visit rescheduled per Section 5.5.4.

Results from the tests should be recorded in the ISF.

## 8.3 Asthma Exacerbations and Respiratory Tract Infections

Acute asthma exacerbation, respiratory tract infections and their treatments may alter the inflammatory profile of the airways. The assessment for acute exacerbation and other acute respiratory tract infection should therefore occur before any other assessments are performed.

During the study, an asthma exacerbation will be defined as a worsening of asthma that leads to any of the following:

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

The start of an exacerbation is defined as the start date of systemic corticosteroids, date of ER or urgent care visits requiring systemic corticosteroids, or date of hospital admission due to asthma, whichever occurs earlier.

The end date of an exacerbation is defined as the last date of systemic corticosteroids, return to baseline dose of OCS for those on chronic OCS, date of ER or urgent care visit, or date of hospital discharge, whichever occurs later.

### 8.3.1 Study Visit Procedures Following Determination of An Acute Asthma Exacerbation or Respiratory Tract Infection

All asthma exacerbations that occur during the treatment and study period must be recorded in the exacerbation eCRF. Asthma exacerbation should be recorded as an AE only if it fulfils any of the criteria for SAE (Section 8.4.7), or the AE leads to IP discontinuation.

Participants who have an asthma exacerbation (worsening of asthma) or respiratory tract infection requiring hospitalization (defined as an admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours e.g., an ER or urgent care

center) will be discontinued from the study (see Section 7.1) and procedures for an Early Study Intervention Discontinuation (E/D) follow-up should be followed as described in the SoA. (Refer to Table 1 for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed).

Participants who have an asthma exacerbation (worsening of asthma) or respiratory tract infection that does not require hospitalization (defined above), but require use of antibiotics and/or systemic corticosteroids (or a temporary increase in a stable oral corticosteroid background dose) for at least 3 days [a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids] should have their visit schedule adjusted per the following guidance, according to when it occurs:

- Before **Visit 1 (V1)**, **this visit** should be rescheduled to occur after resolution of the exacerbation/infection and at least 4 weeks after the last dose of any medication to treat the exacerbation/infection, provided that there are no safety concerns as judged by the Investigator.

- Between **Visit 1 (V1)** and **Visit 3 (V3)**, there will be no changes to the study activities and the SoA should be followed (Table 1).

- Between **Visit 3 (V3) and Visit 4 (V4)**, the participant will be permitted to undergo the study assessments for **Visit 4**, but it should be delayed to ensure an interval between **Visit 4** and the **last dose of antibiotic or OCS, whichever ends later** (or return of OCS dose to previous maintenance dose) of at least 7 days, but no longer than 14 days, per investigator's discretion.

In case of uncertainty related to procedures following an exacerbation, please consult with the AstraZeneca US study team.

## 8.4 Adverse Events and Serious Adverse Events

The Principal Investigator (PI) 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 C.

The definitions of medical device-related safety events, (Medical device (SAE), adverse device effects [ADEs] and SADEs), can be found in Appendix E. (Medical Device deficiencies are covered in Section 8.4.10).

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant'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. See Section 8.4.2 for information on how to follow-up AEs and SAEs.

### 8.4.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from after the participant received the first dose of the study intervention, throughout the treatment period and including the follow-up period (Visit 5, last contact), or up until follow-up for early discontinuation.

SAEs will be recorded from the time of signing of the informed consent form.

If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the serious adverse event to the sponsor.

### 8.4.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in 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 participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Adverse event variables**

'The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Intensity of the AE
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to Investigational Product
- AE caused participant's withdrawal from study (yes or no)
- Treatment for AE
- Outcome
- Causality assessment in relation to study procedure (yes or no)

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- 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
- AE description

### 8.4.3 Causality Collection

The investigator should assess causal relationship between IMP, Investigational Medical devices and/or study procedure and each AE and/or Incident, 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 and Serious Incidents, causal relationship should also be assessed for other medication and study procedures and/or medical devices. 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 C to the Clinical Study Protocol. For medical devices, a guide to the interpretation of the causality question can be found in Appendix E.

### 8.4.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant 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.

### 8.4.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be

summarized in the Clinical Study Report (CSR).

Deterioration as compared to baseline in protocol-mandated vital signs, physical examination and spirometry ($FEV_1$) measurements should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, e.g., dose adjustment or drug interruption).

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

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.

Upper and lower respiratory tract infections will be recorded as AEs.

### 8.4.6 Disease Under Study

Symptoms of disease under study (DUS) are those which might be expected to occur as a direct result of usual, intermittent variations in disease status or response to environmental stimuli (e.g., allergens or weather) or routine pulmonary procedures (e.g., spirometry). Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the investigational product, or is a sign or symptom that is new to the participant or inconsistent with the participant's pre-existing asthma history as judged by the Investigator.

Asthma exacerbation should be recorded as an AE only if it fulfils any of the criteria for SAE (see Section 8.4.7) or if the AE leads to IP discontinuation.

### 8.4.7 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational

product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. Any updated SAE data will be submitted by the Investigator to the sponsor **within 24 hours** of it being available.

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, 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 Electronic Data Capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the electronic AE/SAE reporting is unavailable, AE/SAE should be reported on paper. Fax cover sheet and SAE Report Form (available in the Site File) are to be used.

- Initial notification via EDC does not replace the need for the Investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.

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

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

### 8.4.8 Pregnancy

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

- If the pregnancy is discovered before the study participant has received any study intervention

#### 8.4.8.1 Maternal Exposure

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product 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/birth defect) should be followed up and documented even if the participant was discontinued from the study.

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.4.7) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

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

#### 8.4.8.2 Paternal Exposure

There is no restriction on fathering children or donating sperm during the study.

### 8.4.9 Medication Error, Drug Abuse, and Drug Misuse

#### 8.4.9.1 Timelines

If a medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 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 **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error, drug abuse, or misuse (see Section 8.4.7) and **within 30 days** for all other medication errors.

#### 8.4.9.2 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 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 C4.

#### 8.4.9.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix C4.

#### 8.4.9.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP for medicinal purposes outside of the authorized product information, or for unauthorized IMP, 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 C4.

### 8.4.10 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 E.

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

#### 8.4.10.1 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 E.

#### 8.4.10.2 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.

#### 8.4.10.3 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.

In this study, deficiency observed with any of study treatment medical devices (benralizumab [Fasenra®]) will be collected and reported to the manufacturer using the form available on the Pharmacy manual (for more details please follow up Pharmacy manual).

The third-party medical device deficiency (Spirostik) will be reported by Investigator on the paper form as per the User Manual.

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

#### 8.4.10.4 SADE Reporting

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

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

- The sponsor will review all device constituent deficiencies and determine and

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

#### 8.4.10.5 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 E of the CSP.

## 8.5 Overdose

For this study, any single dose of benralizumab greater than > 30 mg will be considered an overdose.

There is currently no specific treatment in the event of overdose of IP and possible symptoms of an overdose are not established.

- 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 intervention occurs in the course of the study, 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 or 5 calendar days** for overdoses associated with an SAE (see Section 8.4.7) and **within 30 days** for all other overdoses.

## 8.6 Human Biological Samples

The collection and handling of biological samples should be conducted per site's local procedures. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix D.

### 8.6.1 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

#### 8.6.1.1 Determination of Drug Concentration

Pharmacokinetic parameters will not be evaluated in this study. Therefore, the determination of drug concentration will not be conducted.

### 8.6.2 Immunogenicity Assessments

Immunogenicity assessments will not be conducted in this study.

### 8.6.3 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

#### 8.6.3.1 Collection of Samples

Pharmacodynamic parameters will not be evaluated in this study. Therefore, no sample collection will be conducted for this purpose.

## 8.7 Human Biological Sample Biomarkers

### 8.7.1 Collection of mandatory samples for biomarker analysis

Biomarkers will not be evaluated in this study. Therefore, no mandatory sample collection will be conducted for this purpose.

### 8.7.2 Collection of Optional Biomarker Samples

Biomarkers will not be evaluated in this study. Therefore, no optional sample collection will be conducted for this purpose.

### 8.7.3 Other Study Related Biomarker Research

Other study related biomarker research will not be conducted in this study.

## 8.8 Optional Genomics Initiative Sample

Optional Genomics Initiative research will not be a part of this study.

## 8.9 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 Statistical Hypotheses

For the primary and secondary objectives, measures of mean within subject difference in FRI parameters (enumerated in Table 3) between weeks 0 and 13 the null hypothesis is a difference of 0, an assumption based on existing data described in Section 4.2 suggesting untreated participants are likely to exhibit stable or declining primary endpoint values over a similar (12 week) time period.

## 9.2 Sample Size Determination

CCI [redacted]

CCI [redacted]

CCI [redacted]

**Note**: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not assigned in the study, are considered" screen failures", unless otherwise specified by the protocol.

## 9.3 Populations for Analyses

The following populations are defined:

**Table 8 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| Enrolled | All participants who sign the informed consent form |
| Randomly assigned to study intervention | NA (single-arm study) |
| Evaluable | All participants who have completed three doses of investigational product, and have baseline and post-benralizumab treatment study evaluation (PROs, CT scans and spirometry tests) - the evaluable population. |
| Primary analysis population | The portion of the evaluable population that **did not have** an acute asthma exacerbation nor lower respiratory tract infection during the study period will be **the primary analysis population** for the endpoints in this study. |
| Baseline endpoints analysis set | Participants who have baseline measurements and who have had at least one dose of investigational product, irrespectively of whether they discontinued for reasons described in Section 7.1 will be included for analyses conducted on the study population who at least started treatment. |
| Safety analysis set | The Safety analysis set consists of all participants who have received at least one dose of investigational product. |

## 9.4 Statistical Analyses

The statistical analysis plan will be finalized prior to Data Base Lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

### 9.4.1 General Considerations

All continuous variables (including FRI parameters, pre-BD $FEV_1$, pre-BD FVC, CCI [redacted] CCI [redacted]) will be summarized using means, standard deviations and 95% ranges, or medians and inter-quartile ranges, depending on the distributions of the data. Mean changes from baseline in continuous variables will be reported, including asymptotic 95% confidence intervals and standard errors. Categorical data (e.g., CCI [redacted] control CCI [redacted] CCI [redacted] asthma control category) will be summarized as the number and percentage among patients with non-missing data. Descriptive statistics will also be calculated for the data stratified by gender. Unless otherwise stated, all hypothesis tests are two-sided and all hypothesis tests will be performed at a 5% significance level. Analyses will be carried out for

overall patients and subgroups as specified in Section 9.4.4. Data may be log-transformed prior to analysis to reduce skewness of FRI parameters.

## 9.4.2 Efficacy

### 9.4.2.1 Primary Objectives

For the primary objective, a paired *t*-test will be used to determine if there is a significant difference between the mean of untrimmed total mucus volume at TLC at week 0 vs week 13, irrespective of patient characteristics.

Secondary analysis of the primary endpoint (untrimmed total mucus volume at TLC) will be a mixed-effects model to incorporate the repeated measurements (corresponding to the different lobes) for each subject. The outcome of change from baseline in the primary endpoint at week 0 vs week 13 per lobe will be modelled in terms of a fixed effect for lobe and a patient-level random effect to estimate the heterogeneity across lobes. Adjustment will be made for baseline mucus volume per lobe. The fitted model will estimate the average change from baseline in mucus volume at week 0 vs week 13 per lobe.

### 9.4.2.2 Secondary Objectives

For the secondary objective 1, univariate paired *t*-tests and mixed effects modelling will be used to assess whether there are statistically significant differences in the means of secondary FRI endpoints (untrimmed total mucus plugs score at TLC, untrimmed total air trapping at FRC, trimmed distal iVaww at TLC, trimmed distal siVaw at TLC and FRC, and untrimmed total iVlung at TLC and FRC) at week 0 vs week 13, unadjusted for patient characteristics.

Secondary analysis of each secondary endpoint will be a mixed-effects model to incorporate the repeated measurements (corresponding to the different lobes) for each subject. The model will estimate the average change from baseline in secondary endpoint at week 0 vs week 13 per lobe, after accounting for the baseline measurement of the secondary endpoint per lobe and heterogeneity across lobes.

For secondary objective 2, a scatter plot will be used to display values of imaging endpoints (primary and secondary FRI parameters) and conventional lung function measures (pre-BD $FEV_1$ and pre-BD FVC response) at week 0, to get a first indication of the relationship between endpoints at baseline. Spearman's rank correlation coefficients will describe the strength of the association between two endpoints. Pearson correlation will also be used for linear relationships. Regression models will be used to estimate the average increase in imaging endpoints per unit increase in conventional lung function measures, with 95% confidence intervals.

For secondary objective 3, a scatter plot will be used to display changes from baseline at

week 13 in imagine endpoints (primary and secondary FRI parameters) against changes from baseline at week 13 in conventional lung function measures (pre-BD $FEV_1$ and pre-BD FVC response). Both Spearman's rank and Pearson correlation coefficients will describe the strength of the association. If changes from baseline in conventional lung function measures at week 13 are related to baseline values, as indicated by fitted regression models, correlation coefficients will be reported per subgroup defined by baseline value.

A linear regression model for imaging endpoints will be fitted, consisting of a binary explanatory variable (corresponding to week 13). The regression coefficient for time will estimate the change from baseline (week 13 vs week 0) in the imaging endpoint. The model will be fitted with and without the inclusion of the change from baseline in pre-BD $FEV_1$ and pre-BD FVC as individual covariates. Estimated regression coefficients for time from the unadjusted and adjusted models will be compared, to indicate whether the change from baseline in the imaging parameter is explained by changes in pre-BD $FEV_1$ and pre-BD FVC. Estimated regression coefficients for changes in pre-BD $FEV_1$ and pre-BD FVC will be reported, to quantify the average change in each imaging endpoint for every one percent increase in pre-BD $FEV_1$ and pre-BD FVC.

**9.4.2.3** CCI

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### 9.4.3 Safety

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 that will have been released for execution by the Sponsor/designee.

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

The AEs will be presented by system organ class and/or preferred term covering number and percentage of patients reporting at least 1 event and number of events where appropriate. An overview of AEs will present the number and percentage of patients with any AE, AEs with outcome of death, SAEs, 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 the most common AEs.

**Vital signs**

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, Min, Q1, median, Q3, and Max.

Details of vital sign analyses will be provided in the SAP.

### 9.4.4 Other Analyses

Further analyses will be conducted for the secondary objectives related to cross-sectional associations between imaging (FRI) endpoints and conventional lung function measurements ($FEV_1$ and FVC) at week 0. These analyses will use measurements from the study population that includes both participants who completed the study per protocol definition, and those who completed baseline measurements at Visit 1 and had at least one dose of IP irrespectively of whether they discontinued for reasons described in Section 7.1.

CCI [redacted]

The evaluable population (Table 4) will be analyzed for the same outcome measures conducted for the primary analysis population (Table 4).

Additional analyses will be conducted for all outcome measures for both the primary analysis population and the evaluable population for the following subgroups:

- Mucus plugging status: Participants with or without mucus plugs identified at the CT scans (Section 8.1.1.2) at Visit 1 (week 0)
- OCS dependency status: OCS-dependent and Non-OCS-dependent participants as defined by the inclusion criteria #4 (Section 5.1)

Results from subgroup analyses above will be compared with corresponding results from the evaluable population.

## 9.5 Interim Analyses

No interim analyses have been planned for this study.

## 9.6 Data Monitoring Committee

No Data Monitoring Committee will be used in this study.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

# Appendix A Radiation Exposure Calculations

The estimate radiation exposures presented in the following table are based on a selection of CT scanners and is not representative of all CT scanners that can be used for the current study. A CT scanner may be used for the current study as long as it meets the minimum requirements stated in Section 8.1.1.

**Table S1: Estimated radiation exposure using the low radiation scanning protocols recommended for this study based on a selection of CT scanner brands and models from four manufacturers**

| Scanner Type | Estimated radiation per HRCT scan ($CTDI_{vol}$ [mGy] (Effective dose [mSv])) | Estimated radiation for 4 HRCT scans ($CTDI_{vol}$ [mGy] (Effective dose [mSv])) | Scanner selected in CT-Expo |
|---|---|---|---|
| GE Discovery HD750 64 | 4.6 mGy (2.5 mSv) | 18 mGy (10.0 mSv) | *Not applicable* |
| GE LightSpeed VCT 64 slices | 4.5 mGy (2.2 mSv) | 18 mGy (8.8 mSv) | *Not applicable* |
| GE Optima CT 660 | 4.9 mGy (2.5 mSv) | 19.6 mGy (10.0 mSv) | *Not applicable* |
| GE Revolution 128 | 3.8 mGy (1.9 mSv) | 15.2 mGy (7.6 mSv) | Revolution CT (Large body) |
| GE Revolution CT 256 | 3.8 mGy (1.9 mSv) | 15.2 mGy (7.6 mSv) | Revolution CT (Large body) |
| Philips Brilliance 64 | 3.2 mGy (1.7 mSv) | 12.8 mGy (6.8 mSv) | *Not applicable* |
| Philips (Brilliance) iCT | 3.4 mGy (1.8 mSv) | 13.6 mGy (7.2 mSv) | *Not applicable* |
| Philips Ingenuity 128 | 3.3 mGy (1.8 mSv) | 13.2 mGy (7.2 mSv) | *Not applicable* |
| Siemens Somatom Perspective 128 | 4.5 mGy (2.4 mSv) | 18.0 mGy (9.6 mSv) | Siemens Somatom Perspective |
| Siemens Somatom Perspective 32 | 4.5 mGy (2.4 mSv) | 18.0 mGy (9.6 mSv) | Siemens Somatom Perspective |
| Siemens Somatom Perspective 64 Slices | 4.5 mGy (2.4 mSv) | 18.0 mGy (9.6 mSv) | Siemens Somatom Perspective |
| Siemens Somatom Definition 64 | 3.6 mGy (1.6 mSv) | 14.4 mGy (6.4 mSv) | AS series |
| Siemens Somatom Definition 128 | 3.6 mGy (1.6 mSv) | 14.4 mGy (6.4 mSv) | AS series |
| Siemens Somatom Definition 256 | 3.6 mGy (1.6 mSv) | 14.4 mGy (6.4 mSv) | AS series |
| Siemens Somatom Definition Edge 128 | 3.4 mGy (1.4 mSv) | 13.6 mGy (5.6 mSv) | *Not applicable* |
| Siemens Somatom Definition Flash 128 | 3.4 Gy (1.7 mSv) | 13.6 mGy (6.8 mSv) | Tube A |
| Siemens Somatom Sensation 40/64 | 3.1 mGy (1.8 mSv) | 12.4 mGy (7.2 mSv) | *Not applicable* |
| Siemens Somatom Force | 3.6 mGy (1.9 mSv) | 14.4 mGy (7.6 mSv) | BS normal |
| Siemens Somatom Edge Plus | 3.4 mGy (1.4 mSv) | 13.6 mGy (5.6 mSv) | Definition Edge |

| Scanner Type | Estimated radiation per HRCT scan ($CTDI_{vol}$ [mGy] (Effective dose [mSv])) | Estimated radiation for 4 HRCT scans ($CTDI_{vol}$ [mGy] (Effective dose [mSv])) | Scanner selected in CT-Expo |
|---|---|---|---|
| Toshiba Aquillion Prime 160 | 4.1 mGy (2.4 mSv) | 16.4 mGy (9.6 mSv) | Prime (BS medium) |
| Toshiba Aquillion 64 | 6.5 mGy (4.0 mSv) | 26 mGy (16.0 mSv) | Aquillion -8 to -64 |

CT, computed tomography; $CTDI_{vol}$, volume computed dose index.

Note: The calculations for the effective dose strictly apply only for an average male patient with a height of 170 cm (5' 7"), a weight of 70 kg (154 lbs) and a trunk diameter of 28.3 cm. The $CTDI_{vol}$ refers to standardized cylindrical phantoms made from PMMA of diameter 32 cm and is thus independent of patient dimensions. The effective dose is dependent on patient size, therefore these calculations are just an indication. Spiral scans require additional data at the start and the end of the spiral. Given the spiral mode is on, an overranging correction is introduced, which will increase the effective dose. When using CT-Expo, the typical total error in dose calculation is ±10 to ±15% for those quantities which can also be measured ($CTDI_{vol}$, $CTDI_w$ [weighted computed tomography dose index], $DLP_w$ [dose length product]) and ±20 to ±30% for those quantities which can only be derived by using conversion coefficients (effective dose). A manual calculation for the radiation dose was done for a GE Lightspeed VCT and the result corresponds to the calculation of CT-Expo within the accuracy range. A dose estimation report of the Siemens scanner gave a value for the $CTDI_{vol}$ of 3.86 mGy. Calculation by CT-Expo with same scanner settings gave a value of 3.2 mGy. The CT-Expo manual states that the typical total error for $CTDI_{vol}$ lies within a range of 15%. Irvin and Ireland (2014) indicate that a scanner's estimation for the $CTDI_{vol}$ also contains a certain error, varying from -22% to 15% depending on the scanner type. Taking this information into consideration, the values for CT-Expo's calculation and the scanner's estimation are within the error range, providing support that the estimations from CT-Expo gives a good indication for the radiation dose a patient will receive.

**Table S2: Specific settings that were used in CT-expo**

| Settings | Value used |
|---|---|
| U | 100 |
| I | 200 |
| T | 0.6 |
| $N*h_{col}$ | 40 |
| TF | 55 |
| $h_{rec}$ | 0.3 |
| Spiral mode | On |
| Longitudinal dose modulation | On |
| Gender | Male |
| Scan range | 40-70 |
| ICRP | 60 |

$H_{rec}$, reconstructed slice thickness; I, electrical tube current in mA;
ICRP, International Commission on Radiological Protection; $N*h_{col}$, beam width;
t, acquisition time per slice or rotation time (spiral scans); TF, table feed per rotation;
U, kilovolts.

# Appendix B Regulatory, Ethical, and Study Oversight Considerations

## B 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 (e.g., 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 authorizations 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 (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

**Regulatory Reporting Requirements for Serious Breaches**

- Prompt notification by the investigator to AstraZeneca 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 participant or the reliability and robustness of the data generated in the clinical study.
- 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, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the EMA 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 AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

## B 2 Financial Disclosure

Include text related to financial disclosure if not included in another document.

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.

## B 3 Informed Consent Process

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

Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants 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 center.

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

Participants 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 participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

## B 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant 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 and use of their data must also be explained to the participant in the informed consent
- The participant 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.
- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.

- The participant must be informed that in some cases their data may be pseudonymised. The General data Protection Regulation (GDPR) defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

**Personal Data Breaches**

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller[1] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The Investigator should have a process in place to ensure that:

- Site staff or service providers delegated by the investigator/institution are allowed to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- have taken all necessary steps to avoid personal data breaches and

[1] The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission

- have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal Data Breach to participants:

- notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.
- If a personal data breach involving an AstraZeneca's representative device (ie, Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no

access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.

- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

## B 5 Dissemination of Clinical Study Data

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

## B 6 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor 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.
- Monitoring details describing strategy (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 provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized 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 the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

## B 7 Source Documents

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

Data entered in the eCRF 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.

Definition of what constitutes source data can be found in the source data agreement and computerized data checklist for electronic source data.

## B 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 act of recruitment is the first site open and will be the first patient screened.

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

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

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

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

- Discontinuation of further study intervention development

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.

Participants from terminated sites cannot be transferred to another site to continue the study.

## B 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 before submission. 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 C Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## C 1 Definition of Adverse Events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study participant 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 (eg, 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 study intervention has been administered.

## C 2 Definition of Serious Adverse Events

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

- Results in death
- Is immediately life-threatening
- Requires in-participant 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 jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events (AEs) for **malignant tumors** 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 tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, 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.

**Life-threatening**

'Life-threatening' means that the participant 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 participant'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).

**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 oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

**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 participant 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 (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

**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 C 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 C 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 C 2.

## C 3 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 participant 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 no available facts or arguments to suggest a causal relationship, 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.

# C 4 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 IMP that either causes harm to the participant or has the potential to cause harm to the participant.

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

Medication error includes situations where an error:

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

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

- Drug name confusion
- Dispensing error eg, 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 eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

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

- Errors related to or resulting from IRT/RTSM - 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) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

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

**Drug Abuse**

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP 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 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 for medicinal purposes outside of the authorized product information, or for unauthorized IMPs, 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 D Handling of Human Biological Samples

## D 1 Chain of Custody

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

The investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

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 record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives 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

# Appendix E 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 6.1.2 for the list of sponsor medical devices.

## E 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.

## E 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).

## E 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.

## E 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 (e.g., 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 the Sponsor in lieu of completion of the AE/SAE/medical device deficiency form.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. 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 the Sponsor.

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) or USPI / EU SmPC 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 the Sponsor. 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 the Sponsor.

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[2] device or procedures.

- 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;

[2] Investigational device: any device object of the clinical investigation, including the comparators

- 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;
- 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.

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.

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.

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.

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 the Sponsor to 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 the Sponsor 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 the Sponsor within 24 hours of receipt of the information.

## E 5 Reporting of SAEs

**SAE Reporting to the Sponsor via Paper Data Collection Tool**

The SAEs, pregnancies and overdose to be reported in the EDC first. Only report on paper if EDC is unavailable. Fax cover sheet and SAE Report Form (available in the Site File) are to be used.

- Initial notification via EDC does not replace the need for the Investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.

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 paper SAE form available in the Site File.

## E 6 Reporting of SADEs

**SADE Reporting to the Sponsor**

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 the Site File.

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

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. In case of doubts please contact the AZ Study Physician.

The current protocol allows for rescreening of participants for 1 time only if the reason for screen failure was due to a civil crisis, natural disaster, or public health crisis (see Section 5.4). Participants may also reschedule Visit 1 due to a civil crisis, natural disaster, or public health crisis per Section 5.5. Any changes to the allowances for rescreening and rescheduling of visits due to a civil crisis, natural disaster, or public health crisis beyond the current protocol may only be considered at the Sponsor's discretion and Investigators will be informed accordingly.

Changes described in F 1 to F 5 below may only be implemented at the Sponsor's discretion during study disruptions due to any of or a combination 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 participants become infected/quarantined due to SARS-CoV-2 or similar pandemic infection) during which participants 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.

Refer to the Study Instructions for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis for Benralizumab and Study Instructions for At-home or Remote Location Administration of Benralizumab by the Participant and/or His/Her Caregiver for step-by-step guidance.

## F 1 Consent/Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, e.g., telemedicine visits. Consent/reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections F 2 to F 5. Local and regional regulations and/or guidelines regarding consent/reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the

case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining consent/reconsent should be avoided.

## F 2 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix and the associated Study Instructions for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis for Benralizumab, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including virtual or video visits.

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 participants will allow adverse events, concomitant medication, any worsening of underlying asthma symptoms/asthma exacerbations since last contact with the participant to be reported and documented. If applicable, safety procedures will be performed according to the revised SoA in the Study Instructions for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis for Benralizumab.

On-site visits that may be replaced by a Telemedicine Visit only apply for Visit 2 and Visit 3 of this study.

## F 3 At-home or Remote Location IP Administration Instructions

During a civil crisis, natural disaster, or public health crisis, if a site visit is not possible, at-home administration of IP may be performed by the participant or his/her caregiver. The option of at-home IP administration ensures participants' safety in cases of a pandemic where participants may be at increased risk by traveling to the site/clinic. This will also minimize interruption of IP administration during other study disruptions, e.g., site closures due to natural disaster.

At-home IP administration may be conducted for Visit 2 and Visit 3 of this study via a Telemedicine Visit.

**At-home or Remote Location IP Administration by the Participant or His/Her Caregiver**

Prior to at-home or remote location IP administration the Investigator must assess the participant or his/her caregiver to determine whether they are appropriate for at-home or remote location administration of IP. Once the participant or his/her caregiver is deemed appropriate for at-home or remote location administration, he/she must receive appropriate training. All necessary supplies and instructions for administration and documentation of IP administration will be provided. More information related to the visit can be obtained via a telemedicine visit. All process for at-home or remote location IP administration will be witnessed by the Investigator/authorized delegate virtually during a telemedicine visit.

## F 4 Data Capture During Telemedicine Visits

Data collected during telemedicine visits will be captured by the qualified HCP from the study site in the source documents during the visit.

# Appendix G Abbreviations

| Abbreviation or special term | Explanation |
|---|---|
| 3D | 3-dimensional |
| β-HCG | β-human chorionic gonadotropin |
| CCI | CCI |
| ACT | Asthma Control Test |
| ADA | Anti-drug antibody |
| ADE | Adverse device effect |
| ADCC | Antibody-dependent cell-mediated cytotoxicity |
| AE | Adverse event |
| CCI | CCI |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase/transaminase |
| CCI | CCI |
| AST | aspartate aminotransferase/transaminase |
| ATS | American Thoracic Society |
| BD | Bronchodilator |
| BP | Blood pressure |
| BVX | Blood vessel measurements |
| CAD | Computer-aided design |
| CFD | Computational fluid dynamics |
| CFR | Code of Federal Regulations |
| CIOMS | Council for International Organizations of Medical Sciences |
| COPD | Chronic obstructive pulmonary disease |
| CONSORT | The Consolidated Standards of Reporting Trials |
| CCI | CCI |
| CRO | Contract Research Organization |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CT | Computed tomography |
| $CTDI_{vol}$ | Volume computed dose index |
| $CTDI_{w}$ | Weighted computed tomography dose index |
| CTIS | Clinical Trial Information System |

| Abbreviation or special term | Explanation |
|---|---|
| $DLP_w$ | Dose length product |
| DUS | Disease Under Study |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| E/D | Early Study Intervention Discontinuation |
| EDC | Electronic data capture |
| EOT | End of treatment |
| EMA | European Medicines Agency |
| EPAR | European public assessment report |
| ePRO | Electronic patient-report outcome |
| ER | Emergency room |
| ERS | European Respiratory Society |
| EU | European Union |
| FDA | United States Food and Drug Administration |
| FEV1 | Forced expiratory volume in 1 second |
| FRC | Functional residual capacity |
| FRI | Functional Respiratory Imaging |
| FSH | Follicle stimulating hormone |
| FVC | Forced vital capacity |
| GCP | Good Clinical Practice |
| GGT | Gamma-glutamyl transpeptidase |
| GMP | Good Manufacturing Practice |
| Hb | Hemoglobin |
| HBsAg | Hepatitis B surface antigen |
| HCG | Human chorionic gonadotropin |
| HCP | Healthcare professional |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Immunodeficiency virus |
| HLT | High level term |
| HPF | High power field |
| IAD | Internal airflow distribution |
| IB | Investigator’s Brochure |
| IATA | International Airline Transportation Association |

| Abbreviation or special term | Explanation |
|---|---|
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| ICS | inhaled corticosteroids |
| ID | Identifier |
| IEC | Independent Ethics Committee |
| IgE | Immunoglobulin E |
| IL-4R | Interlukin-4 receptor |
| IL-5 | Interleukin-5 |
| IL-5R | Interlukin-5 receptor |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| ISF | Investigator study file |
| IUD | Intrauterine device |
| IUS | Intrauterine hormone-releasing system |
| IV | Intravenous |
| iVaww | Airway wall volume |
| iVlung | Lung volume |
| IWRS | Interactive Web Response System |
| LABA | Long-acting β2 agonists |
| LAMA | Long-acting muscarinic antagonist |
| LLL | Left lower lobe |
| LRI | Lower respiratory infection |
| LTRA | leukotriene receptor antagonists |
| LUL | Left upper lobe |
| MART | Maintenance and reliever therapy |
| MDR | Medical Device Regulation |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMAD | Mass median aerodynamic diameter |
| MRI | Magnetic resonance imaging |
| NA | Not applicable |
| OCS | Oral corticosteroids |
| PI | Principal investigator |

| Abbreviation or special term | Explanation |
|---|---|
| CCI | CCI |
| PROs | Patient-reported outcomes |
| PT | Preferred term |
| Q4W | Every 4 weeks |
| Q8W | Every 8 weeks |
| RBC | Red blood cells |
| RLL | Right lower lobe |
| RML | Right middle lobe |
| RTSM | Randomization and Trial Supply Management |
| RUL | Right upper lobe |
| CCI | CCI |
| SADE | Serious adverse device effect |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARP | Severe Asthma Research Program |
| SC | Subcutaneously |
| SD | Standard deviation |
| CCI | CCI |
| siVaw | Specific airway volume |
| MART | Maintenance and reliever therapy |
| SmPC | Summary of Product Characteristics |
| SoA | Schedule of Activities |
| SOC | System organ class |
| SOP | Standard operating procedure |
| SUSAR | Suspected unexpected serious adverse reactions |
| TLC | Total lung capacity |
| ULN | Upper limit of normal |
| URI | Upper respiratory infection |
| USADE | Unanticipated serious adverse device effect |
| USPI | United States Prescribing Information |
| V | Visit |
| VDP | Ventilation defect percent |
| WBC | White blood cells |

| Abbreviation or special term | Explanation |
|---|---|
| WOCBP | Women of childbearing potential |

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