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

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

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
CCI	CCI
AE	Adverse event
CCI	CCI
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical (Classification)
BD	Bronchodilator
BMI	Body mass index
BVX	Blood vessel measurements
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CCI	CCI
eCRF	Electronic Case Report Form
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computer tomography
ECG	Electrocardiogram
FEV_1	Forced expiratory volume in 1 second
FRC	Functional residual capacity
FRI	Functional Respiratory Imaging
FVC	Forced vital capacity
GINA	Global initiative for asthma
Hb	Hemoglobin
HRCT	High-resolution computer tomography

Abbreviation or Specialized Term	Definition
ICF	Informed consent form
iVlung	Lung volume
iVaww	Airway wall volume
IPD	Important protocol deviation
ISF	Investigator Site File
MedDRA	Medical Dictionary for Regulatory Activities
OCS	Oral corticosteroids
CCI	CCI
PDAP	Protocol deviation assessment plan
PROs	Patient-reported outcomes
CCI	CCI
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
siVaw	Specific airway volume
CCI	CCI
SoA	Schedule of Activities
SOC	System Organ Class
TLC	Total lung capacity
WHODrug	World Health Organization Drug Dictionary

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	12/4/2023	Initial approved SAP	Yes	N/A
List of abbreviations	09/11/2023	New abbreviations added	Yes (v 4.0)	Clarification required
Section 3: Statistical Analysis	09/11/2023	Added information about rounding	Yes (v 4.0)	Clarification required
Section 3.2: Endpoint Analysis	09/11/2023	Changes to endpoints	Yes (v 4.0)	Endpoint changes to CSP v 4.0
Section 3.2.1: Primary Endpoint – Change from Baseline in siVaw Measurements	09/11/2023	Prednisone equivalent added	Yes (v 4.0)	Clarification required
Section 3.6.2: Adverse events	09/11/2023	AEs collection dates specified	Yes (v 4.0)	Clarification required
Section 5: References	09/11/2023	New references added	Yes (v 4.0)	Clarification required
Section 6: Appendix	09/11/2023	New appendix added	Yes (v 4.0)	Clarification required
Section 2.3: General considerations	22/01/2024	Table 2 edited: proposed rank removed; abbreviations added, endpoints with proposed rank >7 removed except CCI CCI	Yes (v 5.0)	Updated as in CSP
Section 3.2: Endpoint analysis	22/01/2024	Table 3 edited, clarification of some endpoints	Yes (v 5.0)	Clarification required
Section 3.2.1: Primary Endpoint – Change from Baseline (Week 0) to week 13 in airway dynamics, using untrimmed total mucus volume at TLC	22/01/2024	Changes to endpoints	Yes (v 5.0)	Endpoint changes to CSP v 5.0
Section 3.2.1.5: Secondary analysis of primary endpoint	22/01/2024	Mixed model equation added	Yes (v 5.0)	Clarification required

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Section 3.1.6.1 Disease characteristics. Definitions and derivations	12/02/2024	Imputation rules added	Yes (v 5.0)	Clarification required
Section 3.2.4 Secondary Endpoint 3	13/02/2024	Analysis set removed, except Primary analysis set	Yes (v 5.0)	Population removed to streamline analysis
Section 3.2.5 Tertiary Endpoint 1	13/02/2024	Analysis set removed, except Baseline endpoints analysis set	Yes (v 5.0)	Population removed to streamline analysis
Section 3.2.6 Tertiary Endpoint 2	13/02/2024	Analysis set removed, except Primary analysis set	Yes (v 5.0)	Population removed to streamline analysis
Section 3.2.3 Secondary Endpoint 2	16/02/2024	Analysis set removed, except Baseline endpoints analysis set	Yes (v 5.0)	Population removed to streamline analysis

1 INTRODUCTION

In addition to bronchoconstriction and airway thickening, mucus plugging is common and often persistent in patients with asthma and seen on Computer Tomography (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. BURAN is a multicentre, single-group, open-label, Phase 4 study. The BURAN study will investigate the short-term benefits of sustained depletion of airway eosinophils by benralizumab, an anti-IL-5R monoclonal antibody, on airway structure and dynamics using FRI in adults with severe eosinophilic asthma.

The purpose of the Statistical Analysis Plan (SAP) is to describe the planned statistical approaches to address the objectives of BURAN, to support the final Clinical Study Report (CSR). The SAP is based on the BURAN Clinical Study Protocol (CSP) version 5.0, dated 08 January 2024.

2 DATA ANALYSIS CONSIDERATIONS

2.1 Timing of Analyses

The analyses will be performed after the end of study. No interim analyses are planned.

2.2 Analysis Populations

The analysis data sets are defined as reported in Table 1.

Table 1 Analysis Data Sets

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

PRO Patient Reported Outcomes

2.3 General Considerations

In this study, Functional Respiratory Imaging (FRI) will be used to measure changes in airway dynamics. The FRI endpoints are defined in Table 2.

Table 2 Functional Respiratory Imaging Parameters

Parameter from Protocol	Description	Parameter from data transfer	Anticipated Data Selection Specifications
Untrimmed total mucus volume at TLC (Primary)	Mucus volume	CCI [redacted]	
Untrimmed total mucus plugs score at TLC (secondary)	Mucus plugs score		
Total air trapping at FRC (secondary)	Air trapping		
Trimmed distal specific iVaww at TLC(secondary)	Airway wall volume		

Parameter from Protocol	Description	Parameter from data transfer	Anticipated Data Selection Specifications
Trimmed distal specific siVaw at TLC (secondary)	Specific airway volume	CCI	
Trimmed distal specific siVaw at FRC (secondary)	Specific airway volume		
Total iVlung at TLC (secondary)	Lung volume		
Total iVlung at FRC (secondary)	Lung volume		
CCI			

CCI, FRC Functional residual capacity, TLC Total lung capacity

2.3.1 General Study Level Definitions

2.3.1.1 Study Periods

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)
- Baseline/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)

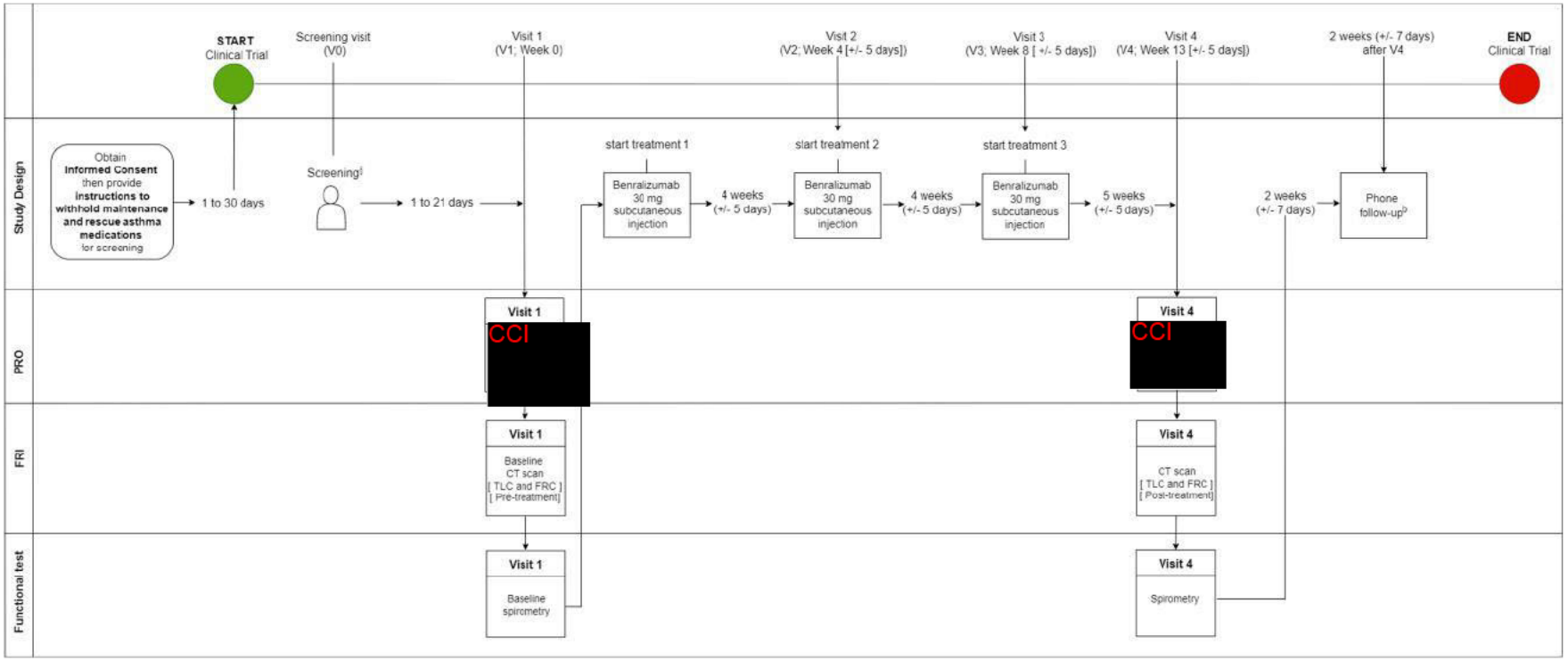
- Visit 4 (V4; Week 13 ± 5 days)
- Follow-up/Visit 5 (V5; 2 weeks [± 7 days] after V4) – phone call follow-up

Refer to Appendix 6.1 for further information on the Schedule of Activities (SoA) to be performed throughout the study.

Participants 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 of the CSP for further information on study intervention after the end of the study.

For all the endpoints, baseline measurement is defined as the last measurement before start of study intervention administration.

Figure 1 Study Design



a CCI [redacted]

b Participants 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 call/Visit 5 or end of treatment follow-up visit for participants who discontinued early in the study.

§: Screening visit includes CCI [redacted], spirometry (with reversibility test if applicable), ECG, and clinical laboratory testing. See SoA (Appendix 6.1) for further details.

2.3.2 Visit Window

The objectives are defined according to outcome measures at Visit 1 (baseline), Visit 2 (Week 4 ± 5 days), Visit 3 (Week 8 ± 5 days) and Visit 4 (Week 13 ± 5 days).

In case more than one measurement is available for any visit window, the one closest to the target day of the visit will be selected for analysis.

In case more than one measurement on the same day is available, the assessment with the earliest time will be selected for analysis.

Visits may be rescheduled within the visit window established in the SoA (Appendix 6.1). 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 of the CSP, the case should be discussed with the AstraZeneca Study Physician and documented in the Investigator site file (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.

2.3.3 Handling of Unscheduled Visits

Any study assessment which is performed outside the visit window for a scheduled visit will be linked to an unscheduled visit. Data collected during unscheduled post-baseline visits will only be reported in the participant listings and will not be considered for summary tables. When unscheduled data are the last obtained before the first study intervention administration, they will be considered as baseline measurements, and will be included in summary tables.

2.3.4 Multiplicity/Multiple Comparisons

Not applicable.

2.3.5 Handling of Protocol Deviations in Study Analysis

Important protocol deviations (IPDs) are those deviations from the protocol identified by the study team as important and requiring summary in the CSR. Methods for identifying IPDs have been defined in the protocol specification assessment plan (PDAP) prior to study start. Protocol deviations will be reviewed periodically throughout the study and the IPDs will be identified and documented.

IPDs are defined as those deviations from the protocol that are likely to have an impact on the completeness, accuracy, and/or reliability of the data for analysis, or that may impact on a participant's rights, safety or well-being. IPDs in this study will be grouped under one of the following four categories:

1 Written informed consent not obtained prior to mandatory study specific procedures, sampling, and analyses.

2 Those who developed discontinuation of protocol specified therapy criteria during the study but remained on protocol specified therapy.

3 Received concomitant medication defined in the protocol as prohibited.

4 Visits or procedures impacted by the Coronavirus disease 2019 (COVID-19) pandemic (eg, missed visits, out of window visits, procedures not done due to the COVID-19 pandemic).

3 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

All continuous variables, including FRI parameters (Table 2), pre-BD FEV_1, pre-BD FVC, CCI [redacted], will be summarized using means, standard deviation (SD) 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 interval (CI). Categorical data (eg, CCI [redacted]) will be summarized as the number and percentage among participants with non-missing data. Descriptive statistics will 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 participants and subgroups as specified in Section 3.2.1.8. FRI parameters may be log-transformed prior to analysis to reduce skewness.

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment.

For continuous data, mean, and upper and lower quartiles will be rounded to one additional decimal place compared to the original data. The SD will be rounded to one additional decimal place compared to the original data. Median, minimum and maximum will be displayed with the same accuracy as the original data. For categorical data, percentages will be rounded to one decimal place, percentages will not be shown for 0, decimal places will not be shown for 100%.

3.1 Study Population

The domain study population covers participant disposition, analysis sets, IPDs , demographics, baseline characteristics, medical history, and prior and concomitant medication.

3.1.1 Participant Disposition and Completion Status

3.1.1.1 Definitions and Derivations

Participants that signed the Informed Consent Form (ICF) will be considered as enrolled participants. For screen failure participants, the reason for screen failure will be reported.

Participants that met all the eligibility criteria will be considered as assigned to the study intervention. Participants with at least one treatment start date will be considered as participants that started the study intervention.

Participants that have the standardized disposition term "Completed" will be considered as having completed the study. Participants that have the standardized disposition term "Screen Failure" will be considered as screening failures. All other participants will be considered as assigned to the study intervention and withdrawn from the study, with the reason reported as the standardized disposition term.

Participants that did not permanently discontinue the study according to the Discontinuation of Study Intervention form will be considered as having completed the treatment. The main reason for study intervention discontinuation will be summarized.

3.1.1.2 Presentation

Participant disposition and completion status will be summarized for all enrolled participants and reported as the number and percentages of:

- screened participants
- screen failures and the reason for screen failure
- participants assigned to the treatment
- participants assigned to treatment but not treated
- participants that started the study intervention, and among these the number and percentage of:
  - participants that completed or discontinued the study intervention
  - participants that completed the study or were withdrawn from the study

3.1.2 Analysis Sets

3.1.2.1 Definitions and Derivations

The populations to be analyzed are defined in Section 2.2 and comprise:

- Participants who completed the study per protocol definition and had no acute asthma exacerbation nor lower respiratory tract infection during the study period (primary analysis population)
- All participants who completed the study per protocol definition (evaluable population)
- Participants who completed baseline measurements at Visit 1 and had at least one dose of study intervention, irrespectively of whether they completed the study or were discontinued for reasons as described in Section 7.1 of the CSP (the baseline endpoints analysis set)

Sub-populations to be analyzed include:

- Mucus plugging status: Participants with (mucus plug score different from 0) or without mucus plugs (mucus plug score equal to 0) identified using CT scans (see Section 8.1.1.2 of the CSP) taken at Visit 1 (Week 0)
- Oral corticosterioids (OCS) dependency status: OCS-dependent and Non-OCS-dependent participants as defined by inclusion criteria 4 (see Section 5.1 of the CSP)

Safety analyses will be performed on the safety analysis set.

3.1.2.2 Presentation

The number of participants included in each analysis set will be reported, as well as the number of excluded participants from each analysis set.

3.1.3 Protocol Deviations

3.1.3.1 Definitions and Derivations

Definitions of IPDs are available in Section 2.3.5.

3.1.3.2 Presentation

The number and percentage of participants with any IPD in the primary analysis set and in the evaluable analysis set will be reported. The number and percentage of participants with any IPD will also be reported according to the category of IPDs listed in Section 2.3.5.

3.1.4 Demographics

3.1.4.1 Definitions and Derivations

Demographic characteristics to be assessed include age (years), sex, race, ethnic group, and country. Age groups 18 to 64 and 65 to 75 will also be presented (for EudraCT reporting).

3.1.4.2 Presentation

Demographics will be summarized for the primary analysis set and the evaluable set. Age will be summarized using mean, SD, median, minimum, and maximum. Age groups, race, ethnic group, and country will be summarized using number and percentage of participants.

3.1.5 Baseline Characteristics

3.1.5.1 Definitions and Derivations

Height (cm), weight (kg), Body mass index (BMI) calculated as: BMI (kg/m^2) = weight(kg)/height$(cm)^2$), and electrocardiogram (ECG) results at screening will be summarized.

3.1.5.2 Presentation

Baseline characteristics will be summarized for the primary analysis set and evaluable. Continuous variables, i.e., height, weight, and BMI, will be summarized using mean, SD, median, minimum, and maximum. Categorical variables, i.e., ECG results and will be summarized using number and percentage of participants.

3.1.6 Disease Characteristics

3.1.6.1 Definitions and Derivations

Asthma history details will be reported, including:

- time since asthma diagnosis
- time since last exacerbation
- number of exacerbations in the previous 12 months and asthma exacerbation details (systemic corticosteroids, increase in a stable oral corticosteroid background dose, associated Emergency Room (ER) visits or hospitalization).
- Global initiative for asthma (GINA) classification
- previously required mechanical ventilation

Time since asthma diagnosis is calculated as follows:

((Screening date – Asthma diagnosis date) + 1)/365.25.

Time since last exacerbation is calculated as follows:

(Screening date – Last exacerbation date) + 1.

If the day of diagnosis is missing then this will be imputed as the 1st of the month. Missing month will be imputed as June, unless diagnosis year is the same as the year of informed consent and the informed consent date is on or before June. Then, we will impute month as the latest month in which the 1st is before the informed consent date.

Completely missing dates will not be imputed; time since diagnosis will be set to missing and reported as n (%) missing. Time since diagnosis will be summarised across patients with a complete or partial data recorded.

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 ER/urgent care visit (defined as evaluation and treatment for < 24 hours in 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)

3.1.6.2 Presentation

Time since asthma diagnosis (days), time since last exacerbation (days), number of exacerbations will be summarized using mean, SD, median, minimum, and maximum. Asthma exacerbation details (systemic corticosteroids, increase in a stable oral corticosteroid background dose, associated ER visits, or hospitalization), GINA classification, and previously required mechanical ventilation will be summarized using number and percentage per category. Summaries will be presented for the primary analysis and evaluable sets.

By-participant listings will be provided for the enrolled participant.

3.1.7 Medical History and Concomitant Disease

3.1.7.1 Definitions and Derivations

Medical and surgical history will be coded according to the most recent MedDRA version and summarized by System Organ Class (SOC) and preferred term.

3.1.7.2 Presentation

Medical and surgical history and concomitant illness will be listed by participant in the enrolled population including description of the disease/procedure, start date and stop date (or ongoing if applicable) based on the safety analysis set.

The number and percentage of participants with any relevant medical history, surgical history, and concomitant illness will be reported overall in the primary analysis set and in the evaluable analysis set, by SOC and preferred term.

Respiratory medical history will be reported in a separate table and listing.

3.1.8 Prior and Concomitant Medications

3.1.8.1 Definitions and Derivations

Prior medication stopped before signing the ICF, as well as all concomitant medications taken during the conduct of the study, will be described.

Prior and concomitant medication will be coded according to the World Health Organization Drug Dictionary (WHODrug), version March 2020 or later.

Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as either prior only, both prior and concomitant, or concomitant only. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications that started and stopped prior to the time of enrolment (Visit 1) will be considered as prior medications. 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 during the study will be recorded as concomitant.

If a medication starts before signing the ICF and stops after signing the ICF then the medication will be classified as both prior and concomitant. Medications will be classified as concomitant only if they have a start date on or after signing the ICF and during the study conduct (ie, during the study follow-up period).

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of signing the ICF. Medications will be assumed to be concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to signing the ICF. If there is clear evidence to suggest that the medication started prior to signing the ICF, the medication will be assumed to be both prior and concomitant, unless there is clear evidence to suggest that the medication stopped prior to signing the ICF. If there is clear evidence to suggest that the medication stopped prior to signing the ICF, the medication will be assumed to be prior only.

3.1.8.2 Presentation

Prior and concomitant medications will be listed by participant in the enrolled population, and will include the following information: reported name, Anatomical Therapeutical Chemical Classification (ATC), and generic drug name, the route of administration, dose, frequency, start date/time, and duration and indication.

A summary of prior and concomitant medications received, by ATC level 4 code and generic drug name overall will be reported on the primary analysis set, evaluable analysis set, and safety analysis set. Prior medications that continue after the date of first dose will also be reported and classified in both prior and concomitant medication groups.

The duration of medication will be calculated as:

- Duration (in hours) = (end date/time – start date/time)/3600; in case date and time is available.
- Duration (in days) = (end date – start date) + 1, in case only the date is provided.

The duration will be reported in days in the listing. For medications with partial or completely missing start date/times and/or end date/times, the duration will not be calculated.

Multiple records for a participant in the same ATC level 4 category and generic drug name will be counted only once.

3.1.9 Study Drug Compliance

3.1.9.1 Definitions and Derivations

Not applicable.

3.1.9.2 Presentation

Not applicable.

3.1.10 Sample Size Analysis

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

CCI

3.2 Endpoint Analyses

This section covers details related to the primary, secondary, tertiary, and safety endpoints, including sensitivity and supportive analyses. A summary of the planned endpoint analyses is provided in Table 3.

Table 3 Summary of Endpoint Analyses

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in Section
Primary objective – To describe the change from baseline in mucus volume at week 13 following treatment with benralizumab, using measurements from untrimmed airways at TLC and irrespective of patient characteristics.					
Primary	Change from baseline (Week 0) at week 13 (± 5 days) in untrimmed total mucus volume at TLC	Evaluable set; Primary analysis population	Included in analysis regardless of treatment discontinuation, any IPD or any prohibited medication (treatment policy); Participants with exacerbations are excluded from the primary analysis set	Unadjusted mean within participant difference in untrimmed total mucus volume calculated as the mean change from baseline (Week 0) at Week 13 (± 5 days).	3.2.1
Secondary objective 1 – To describe the change from baseline in airway dynamics at Week 13 following treatment with benralizumab, as measured by secondary FRI endpoints, irrespective of patient characteristics.					
Secondary	Change from baseline (Week 0) at week 13 in primary and secondary FRI parameters [a]	Evaluable set; Primary analysis population	Included in analysis regardless of treatment discontinuation, any IPD or any prohibited medication (treatment policy); Participants with exacerbations are excluded from the primary analysis set	Unadjusted mean within participant difference, calculated as the mean change from baseline (Week 0) at Week 13 (± 5 days), in listed FRI endpoints.	3.2.2
Secondary objective 2 – To describe the relationship between airway dynamics and conventional lung function measurements, cross-sectionally (at Week 0) and irrespective of patient characteristics.					
Secondary	Baseline (Week 0) relationship between pre-BD FEV_1 and: In primary and secondary FRI parameters [a]	Evaluable set; Primary analysis population; Baseline endpoints analysis set	Included in analysis regardless of treatment discontinuation, any IPD or any prohibited medication (treatment policy). Participants with exacerbations are excluded from the primary analysis set	• Spearman's rank correlation coefficient • Pearson correlation • Graphical summary (scatterplots) • Regression coefficients with 95% CI	3.2.3

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in Section
Secondary	Baseline (Week 0) relationship between pre-BD FVC and: FRI parameters [a]	Baseline endpoints analysis set	Included in analysis regardless of treatment discontinuation, any IPD or any prohibited medication (treatment policy). Participants with exacerbations are excluded from the primary analysis set	• Spearman's rank correlation coefficient • Pearson correlation • Graphical summary (scatterplots) • Regression coefficients with 95% CI	3.2.3
Secondary objective 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.					
Secondary	Relationship between change from baseline (Week 0 to 13) in pre-BD FEV_1 and: FRI parameters [a]	Primary analysis population	Included in analysis regardless of treatment discontinuation, any IPD or any prohibited medication (treatment policy). Participants with exacerbations are excluded from the primary analysis set	• Spearman's rank correlation coefficient • Pearson correlation • Graphical summary (scatterplots) • Regression coefficients with 95% CI	3.2.4
Secondary	Relationship between change from baseline (Week 0 to 13) in pre-BD FVC and: FRI parameters [a]	Primary analysis population	Included in analysis regardless of treatment discontinuation, any IPD or any prohibited medication (treatment policy). Participants with exacerbations are excluded from the primary analysis set	• Spearman's rank correlation coefficient • Pearson correlation • Graphical summary (scatterplots) • Regression coefficients with 95% CI	3.2.4

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in Section
Safety – To monitor the safety and tolerability of benralizumab.					
Safety	Safety and tolerability will be evaluated in terms of AEs, vital signs, and clinical laboratory.	Safety analysis set	Included in analysis regardless of treatment discontinuation, any IPD or any prohibited medication (treatment policy).	Descriptive statistics: number of participants and percentage for categorical variables, mean, SD, median, minimum, maximum, for measured values at each timepoint and changes from baseline	3.6.2, 3.6.3, 3.6.6
CCI [redacted].					

CCI [redacted]

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in Section
CCI [redacted]					
CCI [redacted]					
CCI [redacted]					

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in Section
CCI					

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in Section
CCI [redacted]					

[a] The primary FRI parameter is untrimmed total mucus volume at TLC; secondary FRI parameters include: air trapping at FRC; iVaww at TLC; siVaw at TLC and FRC; iVlung at TLC and FRC; and mucus plugs score (Table 2).

3.2.1 Primary Endpoint – Change from Baseline (Week 0) to week 13 in airway dynamics, using untrimmed total mucus volume at TLC

3.2.1.1 Definition

Table 4 Definition of Primary Endpoint

Population:	Evaluable set; Primary analysis population
Endpoint:	Change from baseline (Week 0) to week 13 in airway dynamics, using untrimmed total mucus volume at TLC
Treatment:	Benralizumab 30mg, 3 doses, once every 4 weeks (at baseline [V1], Week 4 [V2] and Week 8 [V3])
Intercurrent events:	Participant withdrawal, IPD, use of prohibited medicines/substances, asthma exacerbation (Participant with exacerbations will be excluded from the primary analysis set)

Population-level summary:	Unadjusted within participant difference in total mucus volume (specific airway volume) measured at TLC, calculated as the mean change from baseline (Week 0) at Week 13 (± 5 days)

3.2.1.2 Derivations

Change from baseline for each participant will be derived as follows:

mucus volume at Week 13- mucus volume at Week 0

Mean change will be derived across all participants.

3.2.1.3 Handling of Dropouts and Missing Data

The analysis populations will only include participants who have completed 3 doses of study intervention and have baseline and post-benralizumab treatment study evaluation (PROs, CT scans, and spirometry tests). To that end, participants withdrawing before Week 13 and participants with missing mucus volume measurements at Week 0 or Week 13 will not be included in the analysis.

3.2.1.4 Primary Analysis of Primary Endpoint

The distribution of mucus at Weeks 0 and Week 13 will be graphically displayed in a boxplot. If there is evidence of skewness, data will be log-transformed prior to analysis.

For the primary objective, the analysis will be a paired t-test to determine if there is a significant difference between the mean of mucus volume at Week 0 versus Week 13, irrespective of participant characteristics. The level of significance will be set at 0.05 and so the average mucus volume at Week 0 will be interpreted as significantly different from the average mucus volume at Week 13 if the p-value of the t-test is less than a significance level of 0.05.

3.2.1.5 Secondary Analysis of Primary Endpoint

For the secondary analysis of the primary endpoint a mixed-effects model will be employed to incorporate the repeated mucus volume measurements (corresponding to the different lobes) for each subject. The fitted model will provide estimates of the average change from baseline in mucus volume per lobe, with lobe as a fixed effect and a patient-level random effect to estimate the heterogeneity across lobes. Adjustment will be made for the baseline value of mucus volume.

Equation 1 The mixed-effects model will be as follows:

$$y_{ij} = \beta_0 + \beta_{1j} X_{ij} + \beta_2 (baseline)_{ij} + b_{0j} + \varepsilon_{ij}$$

where

- y_{ij} represents change from baseline in mucus volume for subject i lobe j

- β_0 is the intercept
- $\beta_{1j}$is the coefficient for lobe *j*, estimating the average change from baseline in mucus volume for lobe *j*
- X_{ij} is an indicator of whether the mucus volume measurement for subject *i* corresponds to lobe *j*
- $\beta_2$is the coefficient for baseline mucus volume
- $(baseline)_{ij}$ is the baseline mucus volume value for subject *i* corresponding to lobe *j*.
- b_{0j} is the random effect for the *i*th subject
- ε_{ij} is the residual error term

3.2.1.6 Sensitivity Analyses of the Primary Endpoint

Not applicable.

3.2.1.7 Supplementary Analyses of the Primary Endpoint

Not applicable.

3.2.1.8 Subgroup Analyses

The primary endpoint will also be analysed in the following subgroups:

- Mucus plugging status: Participants with (mucus plug score different from 0) or without mucus plugs (mucus plug score equal to 0) identified using CT scans (see Section 8.1.1.2 of the CSP) taken at Visit 1 (Week 0).
- OCS dependency status: OCS-dependent and Non-OCS-dependent participants as defined by the inclusion criteria 4 (see Section 5.1 of the CSP). OCS therapy other than prednisone/prednisolone are allowed provided the average daily dose is equivalent to ≥5 mg of prednisone.

3.2.2 Secondary Endpoint 1 – Change from Baseline in secondary FRI Endpoints

3.2.2.1 Definition

Table 5 Definition of Secondary Endpoint 1

Population:	Evaluable set; Primary analysis population
Endpoint:	Change from baseline (Week 0) in secondary FRI parameters
Treatment:	Benralizumab 30 mg, 3 doses, once every 4 weeks (at baseline [V1], Week 4 [V2] and Week 8 [V3])

Intercurrent events:	Participant withdrawal, IPD, use of prohibited medicines/substances, asthma exacerbation (participants with exacerbations will be excluded from the primary analysis set)
Population-level summary:	Unadjusted mean within participant difference, calculated as the mean percent change from baseline (Week 0) at Week 13 (± 5 days), in listed endpoints

3.2.2.2 Derivations

Not applicable.

3.2.2.3 Handling of Dropouts and Missing Data

The analysis populations will only include participants who have completed three doses of study intervention and have baseline and post-benralizumab treatment study evaluation (PROs, CT scans, and spirometry tests). To that end, participants withdrawing before Week 13 and participants with one of the two FRI measurements missing will not be included in the analysis.

3.2.2.4 Primary Analysis of Secondary Endpoint 1

For each secondary FRI endpoint listed in Table 2, a paired t-test will be used to assess whether there is a statistically significant difference in the mean value at Week 0 versus Week 13, without adjustments for participant characteristics. Data will be log-transformed prior to analysis if there is evidence of skewness.

3.2.2.5 Secondary Analysis of Secondary Endpoint 1

For the secondary analysis of the secondary endpoint, a mixed-effects model will be employed to incorporate the repeated measurements (corresponding to the different lobes) for each subject. The fitted model will be provide estimates of the average percent change from baseline per lobe, with lobe as a fixed effect and a patient-level random effect to estimate the heterogeneity across lobes. The model will adjust for the baseline value of the secondary endpoint. The model will take the same form as described in Equation 1, but with “mucus volume” replaced by the secondary outcome of interest.

3.2.2.6 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

3.2.2.7 Supplementary Analyses of the Secondary Endpoint

Not applicable.

3.2.2.8 Subgroup Analyses

Subgroup analyses will be carried out as described in Section 3.2.1.8.

3.2.3 Secondary Endpoint 2 – Correlation Between Airway Dynamics and Lung Functions Measurements at Week 0

3.2.3.1 Definition

Table 6 Definition of Secondary Endpoint 2

Population:	Baseline endpoints analysis set
Endpoint:	Baseline (Week 0) relationship between: • pre-BD FEV_1 and each FRI parameter (primary and secondary) • pre-BD FVC and each FRI parameter (primary and secondary)
Treatment:	Benralizumab 30 mg, 3 doses, once every 4 weeks (at baseline [V1], Week 4 [V2] and Week 8 [V3])
Intercurrent events:	Participant withdrawal, IPD, use of prohibited medicines/substances, asthma exacerbation
Population-level summary:	• Spearman's rank correlation coefficients • Pearson correlation • Graphical summary (scatterplots) • Regression coefficients with 95% CI

3.2.3.2 Derivations

Not applicable.

3.2.3.3 Handling of Dropouts and Missing Data

Participants with missing baseline (Week 0) measurements do not form part of the analysis populations and so will not be included in the analysis.

3.2.3.4 Primary Analysis of Secondary Endpoint 2

Scatterplots will be used to display values of each imaging endpoint (including: all FRI endpoints in Table 2) against conventional lung function measures (including: 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 each pair of FRI endpoints and conventional lung function measures. If the relationships appear linear, Pearson correlation will also be used. Correlation coefficients will be reported together with 95% CIs and p-values, testing the null hypothesis of no correlation. Standardized residuals will be used to check for linearity. If the linearity assumptions hold and if the two endpoints are correlated as per Pearson's p-value, a linear regression model will be used to estimate the average increase in each imaging endpoint per unit increase in conventional lung function measures, with 95% CIs. Two regression

models per imaging parameter will be performed: one for the association with pre-BD FVC and one for the association with pre-BD FEV_1 at Week 0.

The linear regression model will be as follows:

$$y_i = \beta_0 + \beta_1 x_{1i}$$

where

- y_i is the value of the imaging endpoint at Week 0
- β_0 is the intercept
- x_{1i} is the value of the conventional lung function measure at Week 0
- β_1 quantifies the association as the average change in Y for every one unit increase in x_{1i}

Two models will be fitted for each imaging endpoint, Y, where model (i) takes x_1 to be pre-BD FEV_1 at Week 0 and model (ii) takes x_1 to the pre-BD FVC at Week 0.

3.2.3.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

3.2.3.6 Supplementary Analyses of the Secondary Endpoint

Not applicable.

3.2.3.7 Subgroup Analyses

Subgroup analyses will be carried out as described in Section 3.2.1.8.

3.2.4 Secondary Endpoint 3 - Relationship Between Changes from Baseline in Airway Dynamics and Lung Functions Measurements at Week 13

3.2.4.1 Definition

Table 7 Definition of Secondary Endpoint 3

Population:	Primary analysis population
Endpoints:	Relationship between change from baseline (Week 0 to 13) in: • pre-BD FEV_1 and each FRI parameter (primary and secondary) • pre-BD FVC and each FRI parameter (primary and secondary)
Treatment:	Benralizumab 30 mg, 3 doses, once every 4 weeks (at baseline [V1], Week 4 [V2], and Week 8 [V3])
Intercurrent events:	Participant withdrawal, IPD, use of prohibited medicines/substances, asthma exacerbation (participants with exacerbations will be excluded from the primary analysis set)

Population-level summary:	• Spearman's rank correlation coefficients • Pearson correlation • Graphical summary (scatterplots) • Regression coefficients with 95% CI

3.2.4.2 Derivations

Not applicable.

3.2.4.3 Handling of Dropouts and Missing Data

The populations of interest do not include participants withdrawing before Week 13 and participants with one of the two measurements missing and so will not be included in the analysis.

3.2.4.4 Primary Analysis of Secondary Endpoint 3

For secondary objective 3, a scatter plot will be used to display changes from baseline at Week 13 in each imaging endpoint (including: all FRI endpoints in Table 2) against changes from baseline at Week 13 in each conventional lung function measure (including: pre-BD FEV_1 and pre-BD FVC). Both Spearman's rank and Pearson correlation coefficients will be used to describe the strength of the association between changes from baseline at Week 13 in each imaging endpoint and both of the conventional lung function measures. Estimated correlation coefficients will be reported with corresponding 95% CIs and p-values, testing the null hypothesis of no correlation.

Changes from baseline in conventional lung function measures at Week 13 may be related to baseline values. Therefore, correlation coefficients between each imaging parameter and conventional lung function measure will be reported for the overall populations and for two subgroups, based on dichotomizing at the median baseline value.

To estimate the average change from baseline (Week 13 versus Week 0) in each imaging endpoint, a linear regression model for the change from baseline in each imaging endpoint will be fitted, with adjustment for the baseline (Week 0) measurement of 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. Models including and excluding conventional lung function measures as covariates are defined below and are referred to as adjusted and unadjusted models, respectively.

The adjusted linear regression model will be as follows:

$$y_i = \beta_0 + \beta_1 x_{1\mathrm{i}} + \beta_2 x_{2\mathrm{i}}$$

Where:

- y_i is the change from baseline at Week 13 in the imaging endpoint

- β_0 quantifies the average change from baseline at Week 13 in the imaging endpoint after accounting for the baseline value
- x_{1i} is the baseline value at Week 0 of the imaging endpoint
- β_1 quantifies the association between Y and x_1
- x_{2i} is the change from baseline at Week 13 in the conventional lung function measure
- β_2 quantifies the association between Y and x_2, after accounting for baseline measurements

The unadjusted linear regression model will be as follows:

$$y_i = \beta_0 + \beta_1 x_{1i}$$

Where:

- y_i is the change from baseline at Week 13 in the imaging endpoint
- β_0 quantifies the average change from baseline at Week 13 in the imaging endpoint after accounting for the baseline value
- x_{1i} is the baseline value at Week 0 of the imaging endpoint
- β_1 quantifies the association between Y and x_1, after accounting for baseline measurements

Two adjusted and unadjusted models will be fitted for each imaging endpoint, where the conventional lung function measure is pre-BD FEV_1 for model (i) and pre-BD FVC for model (ii).

Estimated regression coefficients for the intercept, β_0, from the unadjusted and adjusted models will be reported with 95% CIs and p-values, and compared to indicate whether the average change from baseline in the imaging parameter is explained by changes from baseline in pre-BD FEV_1 and pre-BD FVC. Estimated regression coefficients, β_2, for changes in pre-BD FEV_1 and pre-BD FVC will be reported with 95% CIs and p-values, to quantify the average change in each imaging endpoint for every one percent increase in pre-BD FEV_1 and pre-BD FVC.

3.2.4.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

3.2.4.6 Supplementary Analyses of the Secondary Endpoint

Not applicable.

3.2.4.7 Subgroup Analyses

Subgroup analysis is described in Section 3.2.1.8.

3.2.5 CCI [redacted] CCI [redacted])

3.2.5.1 Definition

Table 8 Definition of CCI [redacted] Endpoint 1

Population:	CCI [redacted]
Endpoint:	
Treatment:	Benralizumab 30 mg, 3 doses, once every 4 weeks (at baseline [V1], Week 4 [V2] and Week 8 [V3])
Intercurrent events:	Participant withdrawal, IPD, use of prohibited medicines/substances, asthma exacerbation
Population-level summary:	Spearman's rank correlation coefficients Regression coefficients with 95% CI

3.2.5.2 Derivations

CCI [redacted]

CCI [redacted]

CCI [redacted]’

CCI [redacted]’

CCI [redacted]’

CCI

CCI

CCI

CCI

CCI :

CCI ’

CCI ’

CCI ’

CCI

CCI

3.2.5.3 Handling of Dropouts and Missing Data

Participants with missing baseline (Week 0) measurements do not form part of the analysis populations and will not be included in the analysis.

3.2.5.4 Primary Analysis of CCI Endpoint 1

Correlation (Spearman's rank) coefficients, with 95% CIs, will be reported to describe the strength of the association between each imaging endpoint (including: all FRI parameters) and CCI at baseline (Week 0).

CCI .

CCI

CCI

Linear regression models will be used to model the relationship between each imaging endpoint and CCI s. Regression coefficients for CCI will estimate the average increase in imaging endpoints at Week 0 for CCI of 2-4 and 5-10 versus 0-1 at Week 0. Estimated regression coefficients will be reported together with 95% CIs.

Similarly, linear regression models will be used to estimate the average increase in each imaging endpoint at Week 0, with the 95% CI, for Yes versus No responses at Week 0 to CCI 2, 4, and 8, separately.

We will also estimate the average increase in imaging parameters at baseline for well controlled and partly controlled vs. not well controlled CCI at Week 0), based on linear regression modelling.

3.2.5.5 Additional Analyses of the Other Endpoint

Not applicable.

3.2.5.6 Subgroup Analyses

Not applicable.

3.2.6 CCI [redacted]

3.2.6.1 Definition

Table 9 Definition of CCI [redacted] Endpoint 2

Population:	Primary analysis population
Endpoint:	CCI [redacted]
Treatment:	Benralizumab 30 mg, 3 doses, once every 4 weeks (at baseline [V1], Week 4 [V2] and Week 8 [V3])
Intercurrent events:	Participant withdrawal, IPD, use of prohibited medicines/substances, asthma exacerbation (participants with exacerbations will be excluded from the primary analysis set)
Population-level summary:	• Graphical summary (boxplots) • Descriptive statistics (mean, SD, median, minimum, and maximum) • Spearman's rank correlation coefficient • Regression coefficients (95% CI)

3.2.6.2 Derivations

CCI [redacted] participants will be categorized as follows:

1 Participants with any improvement in total score at Week 13 will be the participants with a total score at Week 13 lower than the total score at baseline.

2 CCI [redacted]

3 Participants showing CCI [redacted]

4 CCI [redacted]

CCI subgroups of participants will be created as follows (Juniper et al., 2005; Juniper at al 2006):

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

2 CCI [redacted]

CCI subgroups of participants will be created as follows:

1 CCI [redacted] CCI [redacted] CCI [redacted] will be the participants with a total score at Week 13 at least 4 points lower than the total score at baseline.

3.2.6.3 Handling of Dropouts and Missing Data

Participants withdrawing before Week 13 and participants with one of the two measurements missing will not be included in the analysis.

3.2.6.4 Primary Analysis of Tertiary Endpoint 2

Participants will complete two versions of the CCI [redacted] (at Visit 4 (Week 13)). The first seven impairment items are evaluated over the past 2 weeks and the last three risk items over the past year for CCI [redacted]

Change from baseline at Week 13 in each imaging endpoint (including: all FRI parameters in Table 2) will be summarized numerically (mean, SD, median, minimum, and maximum) and graphically (using a boxplot), for four CCI subgroups of participants: CCI [redacted]

Change from baseline in each imaging endpoint will also be summarized for two CCI [redacted]

For CCI [redacted] the change from baseline in each imaging endpoint will be summarized for those achieving a CCI [redacted]

Three adjusted and unadjusted models of the form described in Section 3.2.4.4 will be fitted for each imaging endpoint, where the covariate x_2 is CCI [redacted] separate models will also be estimated with the response to items 2, 4, and 8 and their pairwise interactions as covariates.

Estimated regression coefficients for time, β_1, from the unadjusted and adjusted models will be reported with 95% CIs and p-values, and compared to indicate whether the change from baseline in the imaging parameter is explained by changes from baseline in CCI [redacted]. Estimated regression coefficients, CCI [redacted] will be reported with 95% CIs and p-values, to quantify how changes in CCI [redacted] impact on the change from baseline in each imaging endpoint.

Scatterplots will be used to visualize associations between changes from baseline in imaging parameters and questionnaire scores.

3.2.6.5 Additional Analyses of the Tertiary Endpoint 2

Not applicable.

3.2.6.6 Subgroup Analyses

Subgroups are described in Section 3.2.6.4.

3.2.7 CCI

3.2.7.1 Definition

Table 10 Definition of CCI Endpoint 3

Population:	CCI
Endpoint:	
Treatment:	
Intercurrent events:	
Population-level summary:	

CCI

3.2.7.2 Derivations

CCI

CCI

CCI

3.2.7.3 Handling of Dropouts and Missing Data

Participants withdrawing before Week 13 and participants with one of the two measurements missing will not be included in the analysis.

3.2.7.4 Primary Analysis of CCI Endpoint 3

The mean change from baseline (Week 0 to 13) in CCI for a CCI) will be calculated, without adjustment for participant characteristics. A paired t-test will be used to evaluate the statistical significance of the difference in means at Week 0 versus Week 13. The level of significance will be taken to be 0.05.

3.2.7.5 Additional Analyses of the Tertiary Endpoint 3

Not applicable.

3.2.7.6 Subgroup Analyses

Not applicable.

3.3 Pharmacodynamic Endpoint(s)

Not applicable.

3.3.1 Analysis

Not applicable.

3.3.2 Definitions and Derivations

Not applicable.

3.3.3 Presentation

Not applicable.

3.4 Pharmacokinetics

Not applicable.

3.5 Immunogenicity

Not applicable

3.6 Safety Analyses

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

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

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

The domain safety covers exposure, Adverse events (AEs), clinical laboratory, vital signs, and ECG results.

Tables and listings are provided for the safety set.

3.6.1 Exposure

3.6.1.1 Definitions and Derivations

There are only 3 planned study intervention administrations. Study intervention exposure will be reported as the number of treatments effectively administered. This will be three for participants that correctly complete the treatment. In case of any interruption, the actual number of treatment administrations will be reported.

3.6.1.2 Presentation

Treatment exposure will be summarized in the safety analysis set as the number and percentage of participants that were administered with 3, 2, 1 study intervention administrations.

A by-participant listing of study intervention administration data will be provided. Dates and times will be listed for each participant and treatment administration.

3.6.2 Adverse Events

3.6.2.1 Definitions and Derivations

AEs are collected from the time of first dose of IP, throughout the treatment period and until Week 15 safety follow-up period is completed. AE causality is as determined by the reporting investigator. AEs with date of onset on or after the earliest first dose of any of the components of the combination should be considered to be treatment emergent.

AEs will be coded using the most recent version of MedDRA that will have been released for execution by the Sponsor/designee.

Multiple occurrences of an AE in the same participant will only be counted once overall considering start date as the first day of first occurrence and stop date the last day of the last occurrence.

In the case that, during the study, a participant has more than one episode of the same preferred term with different levels of intensity, then the maximum intensity level will be used. The following ordering will be used to define maximum intensity level: Mild < Moderate < Severe.

For each participant and each AE, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to study intervention) will be attributed and used in the by-causality summaries. If severity or causality is missing, a conservative approach for AE assessment (taking into account the worst case) will be followed.

Any AEs with incomplete start and end dates/times will be treated as follows:

- AEs with unknown start times, but with start date known, will be imputed with a time of 00:00, unless the start date corresponds to any given dosing date. In this case the start time will be imputed with the time of dosing. If this results in a start date/time after end date/time of the AE, then the time will also be imputed with 00:00.
- AEs with completely unknown start dates will be imputed with the date and time of dosing unless the end date is known and prior to dosing; in that case the start date will be imputed as the date of screening and a time of 00:00.
- AEs with partially known start dates/times will be treated as follows:

- If only the day is missing, then the day will be imputed with the first day of the month, unless the month and year in which the AE started is a month and year in which study intervention was administered, then the day will be imputed with the first day on which study intervention was administered in that month. If this results in a start date after the end date, then the day will be imputed with the first day of the month.
- If only the month is missing and the year is a year in which study intervention was administered, then the month will be imputed with the first month in which study intervention was administered. If this results in a start date after the end date of the AE, then the month will be imputed with JAN. If the known year part is not a year in which study intervention was administered, then the month will also be imputed with JAN.
- If both the day and month is missing and the year is a year in which study intervention was administered, then the day and month will be imputed with the day and month of dosing. If this results in a start date after end date, then the day and month will be imputed with 01JAN. If the year is not a year in which study intervention was administered, then the day and month will also be imputed with 01JAN.
- If only the year is missing, then the year will be imputed with the year of dosing.

3.6.2.2 Presentation

The AEs will be presented by SOC and/or preferred term covering number and percentage of participants reporting at least 1 event and number of events where appropriate. An overview of AEs will present the number and percentage of participants with any AE, AEs with an outcome of death, Serious adverse events (SAEs), and AEs leading to discontinuation of study intervention. Separate AE tables will be provided taking into consideration the relationship to study intervention as assessed by the Investigator, intensity, seriousness, death, and events leading to discontinuation of study intervention.

AE summaries will be ordered by the international order for SOC and by decreasing frequency for preferred term within SOC.

All reported AEs will be listed along with the date of onset, date of resolution (if AE is resolved), Investigator's assessment of intensity, whether the AE is serious or not, outcome, action taken with study intervention, and possible relationship to study intervention. A by-participant listing of all AE (including AEs before first dose of study intervention) will be provided. This listing will include the following information: study period, verbatim term, MedDRA SOC and preferred term, start date/time, end date/time, time from last dose, intensity, causality, action taken, whether the AE was classified as serious, the outcome of

the AE and the concomitant or additional treatment given, if any. Any AE occurring before the first dose of study intervention and/or the AE assessments that are unresolved at the participant's last assessment in the study will be included in the data listings but will not be included in the summary tables of AEs.

3.6.3 Clinical Laboratory, Blood Sample

3.6.3.1 Definitions and Derivations

Laboratory tests that will be performed and analysed are reported in Table 11.

Table 11 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
Potassium	Creatinine
Sodium	Glucose

3.6.3.2 Presentations

Laboratory values at screening will be listed by participant.

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings. The Investigator will assess whether the values outside the clinical reference range are clinically significant. Clinically significant laboratory values will be recorded by the Investigator as AEs.

Descriptive statistics (for clinical chemistry, haematology) will be reported for both measures values (N, mean, SD, median, minimum, and maximum) .

Additional listings will be presented for urine pregnancy testing, reporting the sampling date and the result (Negative or Positive) for the Pregnancy (Serum or Urine) test.

Clinical laboratory data will be reported in System International units in the CSR.

3.6.4 Clinical Laboratory, Urinalysis

3.6.4.1 Definitions and Derivations

Not applicable.

3.6.5 Other Laboratory Evaluations

3.6.5.1 Definitions and Derivations

Not applicable.

3.6.5.2 Presentations

Not applicable.

3.6.6 Vital Signs

3.6.6.1 Definitions and Derivations

Vital sign parameters include systolic and diastolic blood pressure and heart rate.

3.6.6.2 Presentations

Vital signs data will be listed by participant and timepoint including the date/time of the assessment.

3.6.7 Electrocardiogram

3.6.7.1 Definitions and Derivations

An ECG will be performed at screening to access eligibility for the study.

3.6.7.2 Presentations

ECG data will be listed by participant, including ECG date, interpretation, details for abnormal ECG and clinical significance. ECG data will be summarized as baseline data.

3.6.8 Other Safety Assessments

Not applicable.

4 INTERIM ANALYSIS

Not applicable.

5 REFERENCES

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6 APPENDIX

6.1 Schedule of Activities

Activities	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
COVID-19 vaccination status		X								Section 5.1
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

Activities	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 (continued):										

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
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

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 (continued):										
Urine pregnancy test (WOCBP only)			x d	xd	xd	xd			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
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 treatment 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
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		
Patient Reported Outcomes Assessments:										
CCI [redacted]										

CCI [redacted]

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 with reversibility test post- BD (if needed)[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			Xn	Xn	Xn					Section 6.2

[a] Only for participants who completed 3 doses of study intervention.

[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 participant presents with a positive COVID-19 test result, Visit 0 may be rescheduled as per guidance in Section 5.4 of the CSP. If a participant presents with a positive COVID-19 test result at any time, visits may be rescheduled as per guidance in Section 5.5.4 of the CSP.

[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 of the CSP for further details.

[f] CCI [redacted]

[g] CCI [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: TLC and 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 of the CSP for CT scan procedures and Section 8.1.2 of the CSP 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 of the CSP).

[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 minutes 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.

6.2 Prednisone Equivalent Doses

The following table gives an overview of prednisone equivalent doses (eg 50 mg cortisone is equivalent to 10 mg prednisone) and should be used for converting non-prednisone medications to prednisone equivalent. Multiply the dose of the OCS taken by the subject (in milligrams) in the first column by the conversion factor in the final column to get the equivalent dose of prednisone (in milligrams).

For example: Subject is taking 16 mg of methylprednisolone once daily. To convert to prednisone: 16 mg methylprednisolone × 5/4 = 20 mg prednisone. 16 mg of methylprednisolone once daily is equivalent to 20 mg of prednisone once daily.

Medication preferred term	Equivalent dose	Conversion factor for converting to an equivalent prednisone dose
Prednisone	10 mg	1
Prednisone acetate	10 mg	1
Cortisone	50 mg	1/5
Hydrocortisone	40 mg	1/4
Methylprednisolone	8 mg	5/4
Prednisolone	10 mg	1
Triamcinolone	8 mg	5/4
Betamethasone	1.2 mg	25/3
Dexamethasone	1.5 mg	25/4
Budesonide*	2.25 mg	10/9
Deflazacort*	12 mg	5/6

*equivalent doses and conversion factors based on TULIP study. All others based on information from https://clincalc.com/Corticosteroids/#1 and the following references:

1. Chrousos GP, "Chapter 39. Adrenocorticosteroids & Adrenocortical Antagonists" (Chapter). Katzung BG, Masters SB, Trevor AJ: Basic & Clinical Pharmacology, 11e.

2. Asare K. Diagnosis and treatment of adrenal insufficiency in the critically ill patient. Pharmacotherapy. 2007;27(11):1512-28. PMID 17963461.

3. Glucocorticoids. Facts and Comparisons 4.0. Wolters Kluwer Health, Inc. Conshohocken, PA.

4. Schimmer BP, Funder JW, "Chapter 42. ACTH, Adrenal Steroids, and Pharmacology of the Adrenal Cortex" (Chapter). Brunton LL, Chabner BA, Knollmann BC: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e.

Approval Signatures

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BURAN: Effects of BenralizUmab on AiRwAy DyNamics inSevere Eosinophilic Asthma using Functional RespiratoryImaging Parameters

Statistical Analysis Plan Addendum

Parexel Project Number: 264960

SPONSOR SIGNATURE PAGE

	Signatory
Review/Approval	PPD PPD

Parexel Signature Page

Signature(s) below confirm that the Statistical Analysis Plan Addendum was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD PPD

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	09 Aug 2024	New document
1.1	16 Aug 2024	As per CSR prototype CRM, mucus plug subgroup will be updated for the final analysis.
2.0	22 Aug 2024	New approved version.
2.1	02 Sep 2024	Update to FRI parameters and the addition of the potential post-hoc analysis
3.0	03 Sep 2024	New approved version

1 Changes from the CSP

1.1 Analysis Population

There is a required update to the SAP which will differ from the CSP. It related to the analysis populations in section 2.2 of the SAP. The analysis populations are taken directly form the CSP but has led to a misinterpretation which in turn has led to data being missed from the analysis which could be utilized.

The update relates to the Evaluable analysis set but impacts the Primary analysis set as well. The updated definition is outlined in Table 1.

Table 1 Analysis Data Sets

Population/Analysis Set	Description
Evaluable	All participants who have completed three doses of study intervention and have baseline and post-benralizumab treatment study evaluation in at least one of PROs, CT scans, or spirometry tests – the evaluable population.

The update resolves the issue that a missing PRO, for example, would lead to available spirometry tests or CT scan data not being presented. It has been clarified that only one of these need to be present to be included in the analysis set.

1.2 Visit 4 Window

In sections 2.4.2 of the SAP, visit 4 is defined as Week 13 ± 5 days. There are many participants whose visit 4 date falls outside their window defined in the protocol and the SAP. This means many participants removed from the analysis. It has been decided that the window for visit 4 should be removed entirely as all visit 4 visits should be included in the analysis.

1.3 Mucus Plug Subgroup

In section 3.1.2 of the SAP, sub-populations are outlined. The first of which is mucus plugging status. It is stated that a subgroup analysis will be conducted on those participants with (mucus plug score different from 0) and without (mucus plug score equal to zero) mucus plugs. In the final analysis this is to be updated to participants with greater than or equal to 4 mucus plugs and participants with strictly less than 4 mucus plugs.

1.4 FRI Parameters

Two secondary FRI parameters that are outlined in the protocol will be replaced by new ones in the final analysis. The two that are set to be replaced are listed below:

Table 2 Functional Respiratory Imaging Parameters (old)

Parameter from Protocol	Description	Parameter from data transfer	Anticipated Data Selection Specifications
Trimmed distal specific siVaw at TLC (secondary)	Specific airway volume	CCI [redacted]	
Trimmed distal specific siVaw at FRC (secondary)	Specific airway volume		

They will be replaced by the following:

Table 3 Functional Respiratory Imaging Parameters (new)

Parameter from Protocol	Description	Parameter from data transfer	Anticipated Data Selection Specifications
Untrimmed distal iVaw at TLC (secondary)	Airway volume	CCI [redacted]	
Untrimmed distal iVaw at FRC (secondary)	Airway volume		

The rationale for this change is that there have been more and more insights in the mode of action of biologics in severe asthma. These compounds have greater effects on airway recruitment that can be related to reduced mucus plugging and decreased airway inflammation. In the past, FRI has been used in multiple studies evaluating the effects of inhaled medication in asthma, which

were used as a base when developing this protocol initially several years ago. Those compounds led to greater reductions in airway constriction, which would mostly be relevant when looking at trimmed airways, but more evidence became available that a reduction in bronchoconstriction is not the main driver for biologics. By focusing on the absolute airway volumes from untrimmed airway models there is greater understanding of the effects related to the airways opening up and bringing them within scan resolution after treatment.

1.5 Post-hoc Analysis

A post-hoc descriptive analysis may be conducted on airway wall thickness (the average thickness in mm calculated using an integral-based method. This endpoint is derived from distal airways, i.e., airways distal from the 3rd bifurcation) and Pi10 (the average square root of the cross-sectional wall area of a hypothetical airway of 10-mm lumen perimeter. This endpoint is also derived from distal airways).

Currently, airway wall volume (siVaww) is added in the SAP as an estimate for wall thickness. Quantitative measurements of airway wall volume and morphology have a robust history in the study of obstructive lung diseases, due to their demonstrated ability to detect subtly, spatially limited changes in airway patency related to inflammation, bronchoconstriction/dilation, and the presence of excess mucus. A shortcoming of this method is that it is influenced by airway diameter, i.e., if an airway is dilated its apparent wall volume will spuriously increase. Therefore, alternative endpoints have been developed that reflect the airway wall using different approaches: airway wall thickness (in mm) and Pi10.

Previous studies have shown that anti- IL-5 therapy may impact the extracellular matrix compound in the reticular basement membrane and the airway smooth muscle mass in the airway wall. Quantitative CT-derived measurements are therefore an important non-invasive tool to detect changes in airway wall thickness that may reflect a reduction in airway remodelling.

2 CHANGES TO THE STATISTICAL ANALYSIS PLAN

2.1 Baseline Definition

In Section 2.3.1 of the SAP, the baseline definition is outlined. It has been agreed, cross-functionally, that this definition should be updated in order to include those whose measurement was taken after study intervention of the same day. Hence, the updated baseline definition is:

- Baseline measurement is defined as the last measurement on or before the start day of study intervention administration.

2.2 Time Since Asthma Diagnosis

Section 3.1.6 of the statistical analysis plan provides an equation for the time since asthma diagnosis in years. This will be presented in months in the final TLF shells document so an updated equation for time since asthma diagnosis is.
Time since asthma diagnosis is calculated as follows:

(Date of Screening Visit 1 – Date of asthma diagnosis)/30.4375

2.3 Partial Dates for OCS Dependency

Section 3.2.1.8 of the statistical analysis plan (SAP) stated that the subgroup for the primary analysis is OCS dependency status. The definition of which is provided in Section 5.1 of the CSP, inclusion criteria number 4. The definition relies on being able to calculate how long each subject is OCS dependent but there are currently no rules for dealing with partial dates. Hence the following imputation rules for partial/missing dates will be applied to determine OCS dependency status:

2.3.1 Day is missing

For missing day there are two cases: Condition 1; both days are missing from the start and end date, Condition 2; day is missing from just one of the dates. In order to determine if the two dates are greater than or equal to 3 months apart, both the first day of the month and the last day of the month will be imputed. Then the OCS dependency time will be calculated for each condition:

- Condition 1:
  - Start date is imputed with the first day, end date is imputed with the last day
  - Start date is imputed with the last day, end date is imputed with the first day
- Condition 2:
  - Start day is imputed with the first day
  - Start day is imputed with the last day
  - End date is imputed with the first day
  - End date is imputed with the last day

If one of the above bullet points in each condition lead to the OCS duration being less than 3 months then OCS dependency cannot be determined. If all of the above bullet points for each condition lead to the calculation of duration greater than or equal to 3 months then it can be determined that OCS dependency was greater than or equal to 3 months.

2.3.2 Month is Missing

If the month is missing, then the duration of OCS dependency cannot be determined.

2.3.3 Year is missing

If only year is missing, then the year 2024 will be imputed solely for the duration calculation. The following intervals will determine OCS duration from the calculation OCS end date – OCS start date:

- 0<and<3 months: OCS dependency cannot be determined.
- >= 3 months: OCS duration is greater than or equal to 3 months.
- -12< and <-8: OCS dependency cannot be determined.
- -8<=and <=0: OCS duration was greater than or equal to 3 months.

These rules for partial dates can also be applied to determining the OCS dose relative to the screening visit.

2.4 How to deal with Overlapping OCS Dependency

There is no clearly defined rule for calculating OCS dependency for subjects who were taking multiple OCS medication that were overlapping. As a result, the following rules for overlapping medication will be followed. If a subject was taking multiple OCS medications at the same time, the duration of treatment will be:

latest stop date of the overlapping medications - earliest start date of the overlapping medications.

2.5 Last Exacerbation Partial Date

Section 3.1.6.1 of the SAP outlines definitions for both time since asthma diagnosis and time since last exacerbation but only gives imputation rules for partial dates of asthma diagnosis. Therefore, partial date rules for exacerbation dates need to be outlined. The rules are similar to diagnosis imputation:

If the day of diagnosis is missing, then this will be imputed as the 1st of the month. Missing month will be imputed as June, unless diagnosis year is the same as the year of informed consent and the informed consent date is on or before June. Then, we will impute month as the latest month in which the 1st is before the informed consent date.

Completely missing dates will not be imputed; time since diagnosis will be set to missing and reported as n (%) missing. Time since diagnosis will be summarized across patients with a complete or partial data recorded.

If the year is missing, then the time since last exacerbation will be reported as unknown.

2.6 Visit 4 Window

In sections 2.4.2 of the SAP, visit 4 is defined as Week 13 ± 5 days. There are subjects who have visit 4 outside of this window and given the small number of subjects it has been decided to be more flexible on which visits are allowed in the analysis. Although visits outside of the window will still be considered a protocol deviation we have the following classification:

- Up to five days outside of the window will be a non-important PD.
- Beyond five days outside of the window will be considered an important.

2.7 Linear Regression Model

In SAP sections 3.2.4 and 3.2.6, it states that more than just the intercept should be displayed in the final outputs however it is the intercept which is of interest and should be reported.

Linear regression models that have a population n < 10 will not be shown in the final outputs.

Throughout the linear regression sections of the SAP there is certain wording that requires more clarity. So, the following sections outline the number of model that should be used for each endpoint.

2.7.1 Secondary Endpoint 3 - Relationship Between Changes from Baseline in Airway Dynamics and Lung Functions Measurements at Week 13

The use of the word unadjusted in the SAP causes confusion over the number of models. Instead, the number of models is outlined explicitly. Three linear models will be fitted for each imaging parameter, where the endpoint will be change from baseline to week 13 in the imaging parameter:

- Model 1: Adjustment for baseline measurement of imaging parameter only
- Model 2: Adjustment for baseline measurement of imaging parameter and for change from baseline to week 13 in pre-BD FEV1
- Model 3: Adjustment for baseline measurement of imaging parameter and for change from baseline to week 13 in pre-BD FVC

2.7.2 CCI [redacted]

Table 4outlines the models that are expected for the analysis of tertiary endpoint 1.

Table 4 Model Details for CCI [redacted] Endpoint 1

CCI [redacted]

Should there be no data for the assigned reference category then the most abundant category will be assigned as the reference.

2.7.3 CCI [redacted]

Table 5 outlines all the of models expected for tertiary endpoint 2

Table 5 Model Details for CCI Endpoint 2

2.8 Decimal Place Rules

2.8.1 Derived parameters

Derived parameters such as CCI require specific decimal place rules as the ones currently defined in SAP section 3 are not appropriate. Therefore, the mean, min, max, Q1 and Q3 should be rounded to 2dp, SD to 3dp.

2.8.2 Linear regression parameters

Specific rules for decimal places for the linear regression parameters are not outlined in section 3 of the SAP. So, the regression coefficient and the confidence interval should be rounded to 2dp, the p-value and SD to 3dp.

Mucus volume rules are slightly different and are specified in section 2.11.2.

2.8.2.1 Raw data exceeding 4 decimal places

In situations where the decimals places in the raw data exceed 4 decimal places then all summary statistics will be rounded to 4 decimal places

2.9 Covariance Structure

The following process for determining covariance structure, for the analysis of lobe dependency models, will be applied to the primary endpoint, mucus volume for the overall model in the evaluable analysis set.
This is the structure that will then be used for the rest of the analysis of lobe dependency models (section 3.2.3 of the SAP). An unstructured covariance structure should be implemented first to see if the model converges. If this fails to converge then the best fitting model from the following should be used; compound symmetry (CS), Toeplitz (toep), Variance components (VC), Heterogenous compound symmetry (CSH), Heterogenous Toeplitz (toeph), autoregressive(1) (AR(1)) and Heterogenous autoregressive(1) (ARH(1)).
To determine the best fitting model, all these structures will be tested to see if any of them converge. And that the Hessian matric is positive definite. Of the ones that converge, those with the lowest AIC value will be used in the analysis.

2.10 CCI [redacted]

CCI [redacted]

2.11 Mucus Volume

Mucus volume hasn't previously been presented on previous studies the way it is here. As a result, the rules outlined in the SAP aren't quite appropriate for this parameter. Below are details specific to mucus volume that will be followed when presenting data related to mucus volume.

2.11.1 Summary Statistics

In section 3.1.1 of the SAP, it outlined decimal place rules for continuous data that are based around the number of decimal places that appear in the data. Mucus volume is outlined in the data to up to 9 decimal places. Therefore, the current decimal place rules aren't quite appropriate to follow when summarising this parameter.

For mucus volume data, all summary statistics will be rounded to 4 decimal places.

2.11.2 Regression Coefficients

The regression coefficient precision that is outlined above in section 2.8.2 is not appropriate for mucus volume as some of the detail is lost when rounding to 2dp. Therefore, the regression coefficient for mucus volume will be rounded to 3dp.

2.11.3 Skewed Data

Mucus volume data that is skewed would be log-transformed according to SAP section 3.2.1. This data can be zero however, so a log plus one transformation will be used if needed. That is, each value of the data will be increased by one and then the log-transformation will be applied. The Skewness of the data is determined by checking box plots of the data and seeing if the mean deviates from the median greatly and if there is asymmetry between the quartiles.

Specific airway volume and airway wall volume are the only other FRI parameters that need to be considered for possible transformation. Should it be determined that a transformation is required the rules in SAP section 3.2.1 should be followed.

2.12 Vital Signs

In section 3.6.6.2 of the SAP, it states that vital signs data will be listed only. This contradicts the CSP. Therefore, summary tables of vital sign results will be generated to align the analysis and the protocol.

2.13 Listings

In Sections 3.1.7 and 3.6.7, it is stated that medical and respiratory history and ECG listing will be presented in the final analysis. These outputs are not to be generated for the final TLF package.

In SAP section 3.6.3, it is stated that the pregnancy result is to be listed regardless of whether it is positive or negative. It has since been decided that only positive results will be shown in the final analysis.

2.14 Incomplete Scans

During the dry run it was noted that some participants had baseline definitions of a subset of the FRI parameters. This incompleteness led to them being excluded from further assessment. The

expectation was that if a scan was performed that all FRI parameters would be measured. This inconsistency has resulted in the following update.

Those participants who have incomplete FRI parameters and are missing their baseline or Week 13 assessment will be excluded from the analysis of those parameters. They will, however, remain in the analysis population.

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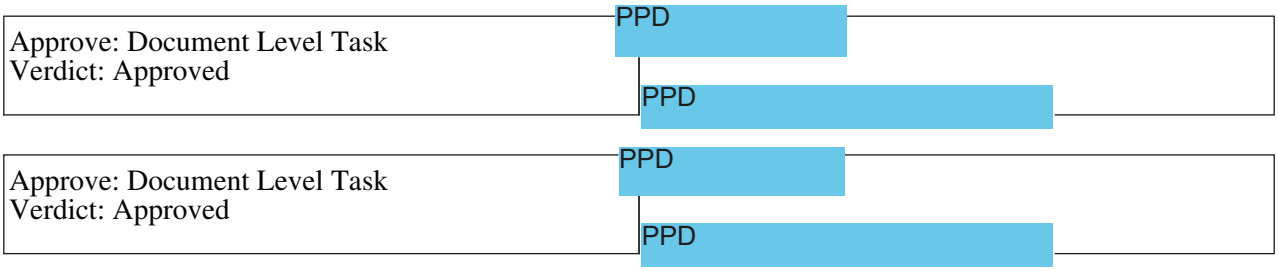

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