STATISTICAL ANALYSIS PLAN	
Study Code	D5985C00003
Edition Number	2.0
Date	3-Jun-2024

A Randomized, Double-Blind, 12-Week (with an Extension to 52 Weeks in a subset of Participants), Multi-Center Study to Assess the Safety of Budesonide, Glycopyrronium, and Formoterol Fumarate (BGF) Delivered by MDI HFO Compared to BGF delivered by MDI HFA in Participants with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	adverse event
AEOSI	adverse event of special interest
ATC	Anatomic Therapy Class
ATS	American Thoracic Society
AV	atrioventricular
BGF	budesonide, glycopyrronium, and formoterol fumarate
BID	twice daily (*'bis in die'*)
BMI	body mass index
CAT	COPD Assessment Test
CDL	clinical data lock
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	chronic obstructive pulmonary disease
CRF	Case Report Form
CSP	Clinical Study Protocol
CTCAE	Common Terminology Criteria for Adverse Events
DAE	discontinuation due to AE
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ERS	European Respiratory Society
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
hCG	human chorionic gonadotropin
HFA	hydrofluoroalkane
HFO	hydrofluoroolefin
ICS	inhaled corticosteroid
IP	investigational product
IPD	important protocol deviation
IRT	Interactive Response Technology

LABA	long-acting beta2-agonist
LAMA	long-acting muscarinic antagonist
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MDI	metered-dose inhaler
PB	paradoxical bronchospasm
PT	preferred term
QTcF	QT corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SABA	short-acting beta2-agonist
SAMA	short-acting muscarinic antagonist
SAP	Statistical Analysis Plan
SOC	system organ class
TC	telephone contact
ULOQ	upper limit of quantitation
VPC	ventricular premature contractions

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	20Dec2022	Initial approved Statistical Analysis Plan (SAP)	Yes	Initial version 03 June 2022
Other	03Jun2024	• Study changed from having two clinical data locks (CDLs) (the first at week 12) to just one at Week 52. • Unblinded interim reporting removed. • Definitions of baseline updated. • Calculation of study compliance updated. • Clinical laboratory parameters updated. • Minor editorial changes were made to correct grammar, spelling, flow of presentation. • Calculation of confidence interval of EAIR difference updated. • ECG and Holter analyses updated. • Visit windows updated for spirometry, ECG, and Holter. • Removed End of Study Definition section (covered in CSP and not relevant to analysis). • Added Exposure section.	Yes	Clinical Study Protocol (CSP) version 2.0 14 Dec 2023

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D5985C00003 supporting the Clinical Study Report (CSR). The reader is referred to the Clinical Study Protocol (CSP) Version 2.0 and the Case Report Form (CRF) for details of study conduct and data collection.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

- The CSP refers to Bronchodilator Reversibility; this is referred to as Bronchodilator Responsiveness in the SAP as it will be reported as such.

- The CSP states baseline for 12-lead resting digital ECG will be defined as the mean of the latest triplicate measurements extracted from the Holter monitor at 60 minutes prior to dosing at Visit 3. Instead, the mean of all available triplicate measurements will be taken (section 3.3.1).

- The CSP states that for digital 12-lead Holter ECG, summary statistics for raw values and changes from baseline in QTcF intervals will be calculated. Summary statistics will be presented for rhythm parameters other than QTcF intervals, since QTcF intervals will be summarised for the 12-lead resting digital ECG.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Analysis Populations

3.1.1 Enrolled Analysis Set

All participants who sign the informed consent form (ICF).

3.1.2 Randomised Analysis Set

All enrolled participants who are randomised to one of the study treatments.

3.1.3 12-Week Safety Analysis Set

The 12-week Safety Analysis Set is defined as all participants who were randomised to study treatment and received at least one inhalation of study drug, irrespective of their protocol adherence and whether they would continue treatment for a total of 52-weeks. Participants will be analysed according to their treatment received. The actual treatment is defined as the study treatment that the participant received the most.

3.1.4 52-Week Safety Analysis Set

The 52-week Safety Analysis Set is defined as all participants who were randomised to study treatment and received at least one inhalation of study drug, and were pre-specified at

randomisation to continue treatment for a total of 52-weeks, irrespective of their protocol adherence. Participants will be analysed according to their treatment received. The actual treatment is defined as the study treatment that the participant received the most.

3.2 Timing of Analyses

Prior to CSP v2.0, two separate Clinical Data Locks (CDLs) and correspondingly two separate study reports were planned. Under CSP v2.0, there will now be one CDL and a single study report containing the analyses of the two study periods (12-week and 52-week).

Listings and key subject information tables will be presented for all subjects in the 12-week safety analysis set for the 0 – 52 weeks study period.

Week 12 Analysis

This will be performed for all participants in the 12-week safety analysis set. For participants who were pre-specified at randomisation to receive only 12 weeks of study treatment, all data (including the Week 14 TC) will be included. For participants who were pre-specified at randomisation to receive 52 weeks of treatment, all data up to and including the Week 12 visit will be included; data beyond Week 12 visit will be excluded as a Week 14 TC will not be performed. For participants who were pre-specified to receive 52 weeks of treatment, but who discontinue from the study either at the Week 12 visit or any visit prior, all data available through the discontinuation date (even if the withdrawal visit happens after Week 12) will be included.

Week 52 Analysis

This will be performed for all participants in the 52-week safety analysis set, and will include all data collected for these participants during the 52-week treatment period. Data from Week 54 TC will be included. There will not be Week 14 TC data because participants in the 52-week safety analysis set will not have this visit according to CSP.

3.3 General Considerations

Analyses will be performed by Everest with Sponsor oversight. Categorical variables will be summarised using frequencies and percentages, where the denominator for calculation is the number of participants included in the underlying analysis set population unless otherwise specified. Continuous variables will be summarised with descriptive statistics using the number of available observations, mean, standard deviation, median, minimum, and maximum, and quartiles where appropriate.

For continuous data, mean, standard deviation, median, first quartile (Q1), and third quartile (Q3) will be rounded to 1 additional decimal place compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data. Confidence intervals (CI) will be presented with the same precision as the estimate. For derived continuous data, unless otherwise specified, the decimal places displayed will be 1 more than the least number of decimal places among the raw data used for calculation – for example, height has values 167.75 and 180.5, weight has values 102.25 and 145.275, then body surface area will have two decimal places, which is one more than the least number of decimal places (180.5) among the raw data. For categorical data, percentages will be rounded to 1 decimal place.

Study day is calculated as date of assessment/event – date of randomisation + 1 if date of assessment/event is on or after randomisation, and is calculated as date of assessment/event – date of randomisation if date of assessment/event is prior to date of randomisation.

AEs will be coded using the latest MedDRA dictionary [version 26.1 (or a later version if updated during the study)] available at the time of CDL.

SAS® version 9.4 will be used for all analyses.

3.3.1 Definition of Baseline

Baseline for Spirometry

Baseline for spirometry is defined as the measurements obtained 30 minutes prior to study intervention administration at randomisation. If the measurements obtained 30 minutes prior to randomisation are missing, the last non-missing pre-dose measurement during screening visits will be used. Note that this differs from baselines used in assessment of paradoxical bronchospasm, as described in section 4.2.2.1.

Baseline for 12-lead Resting Digital ECG Parameters

For analysis of the 12-lead resting digital ECG, baseline will be defined as the mean of the triplicate measurements extracted from Holter at 60 minutes pre-dose on Visit 3. If multiple sets of triplicate measurements are available for the timepoint, baseline will be defined as the mean of all of the available measurements. Assessments that are not evaluable will be excluded.

Baseline for Digital 12-lead Holter ECG recordings

For Digital 12-lead Holter ECG data, two baseline periods prior to randomisation (pre-Visit 3) are defined as follows:

- Baseline 1: the first complete continuous 4-hour period after start of recording pre-Visit 3
- Baseline 2: the period from start of recording pre-Visit 3 until first IP administration.

Baseline 1 will be considered missing if less than 2 hours of continuous recording during that period are available. Baseline 2 will be considered missing if less than 8 hours of continuous recording during that period are available. See section 4.2.5.1 for details of the selection of Holter recordings for analysis.

Baseline for COPD Assessment Test

For CAT data, baseline is defined as the CAT assessment at Visit 1.

Baseline for Clinical Laboratory Parameters

Baseline for laboratory parameters is defined as the last available value prior to dosing on the day of or prior to randomisation.

Baseline for Vital Signs

Baseline for vital signs is defined as the last available value prior to dosing on the day of or prior to randomisation.

3.3.2 Visit Windows

For visit-based analyses, variables are summarised based on data from scheduled or repeat visits (including premature treatment discontinuation visits) by mapping the visit date to an analysis visit window irrespective of the visit's label.

The adjusted analysis-defined windows for 12-lead resting digital and safety ECG, continuous Holter recordings, clinical laboratory, vital sign, spirometry and CAT score endpoints are summarised in **Table 1**. This does not apply to Adverse Event endpoints. See sections 3.3.2.1 and 3.3.2.2 for different windowing to be applied for some 12-lead resting digital and safety ECG and spirometry visits.

Table 1 Visit Windows

Analysis Visit Window	Scheduled Target Study Day	Study Day Range
Screening (Visit 1)	-14 to -7	N/A[a, b]
Screening (Visit 2)	-7 to -1	N/A[a, b]
Randomisation (Visit 3)	1	≤1 [b]
Week 4 (Visit 4)	28	14 to 42
Week 8 (Visit 5)	56	43 to 70
Week 12 (Visit 6)	84	71 to 98
Week 26 (Visit 7)	182	140 to 231
Week 40 (Visit 8)	280	232 to 322
Week 52 (Visit 9)	364	323 to 406

a. No window applied. Analysis visit window is assigned based on the nominal visit label.
b. Except for Spirometry and ECG data – see sections 3.3.2.1 and 3.3.2.2.

If multiple assessments are recorded within a single analysis visit window, the following rules will be applied. These rules will not be applied for the baseline definitions described in section 3.3.1 and in this section.

- If there are observations from two or more visits within the same window, then the non-missing set of observations from the visit closest to the target study day will be used in the analysis, except for spirometry tests, 12-lead resting digital ECG and continuous Holter ECG where the latest available assessments within the window after aligning with dose time (as defined in Table 2 and Table 4, and section 3.3.2.4) will be used.

- If there are observations from two or more visits that are equidistant from the target study day, then the non-missing set of observations with the earliest collection date will be used in the analysis, except for spirometry tests, 12-lead resting digital ECG and continuous Holter ECG after aligning with dose time (as defined in Table 2 and Table 4, and section 3.3.2.4) where the latest collection date will be used.

- If two observations are collected on the same day then the observation with the earliest collection time will be included in the analysis, unless the observations are dependent on study time window (e.g. spirometry and 12-lead resting digital ECG), then the observation that is closest to the target time within the respective time window (as defined in Table 2 and Table 4) will be used.

3.3.2.1 Spirometry Tests

Forced expiratory spirometry manoeuvres for FEV_1, FVC, FEV_1/FVC ratio as defined in the 2019 ATS/ERS guidelines will be performed in accordance with ATS/ERS acceptability and repeatability criteria, following the schedule presented in Table 2. If multiple assessments occur in the same time window in Table 2 below for Visit 3 - Visit 9 the assessment that is closest to the target time within the respective time window will be used as the analysis value for the given window.

Table 2 Time Windows for Spirometry Tests

Visit	Analysis Target Time	Time Interval for the Analysis Time Window
Visit 3-9	30 minutes pre-dose	<0 min post-dose
	5 minutes post-dose	0 to <14 min post-dose
	15 minutes post-dose	14 to <25 min post-dose
	30 minutes post-dose	25 to <45 min post-dose
	60 minutes post-dose	45 to <75 min post-dose

During the withdrawal visit, trough spirometry will be conducted approximately 60 to 30 minutes prior to standard time for the morning dose of discontinued study intervention or new standard COPD maintenance treatment.

Spirometry tests are also conducted during screening visits 1 and 2. The analysis visit windows for visits 1 to 3 will be assigned based on the visit label and number for these data as defined in Table 3.

Table 3 Visit Windows for Screening and Randomisation

Analysis Visit Window	Scheduled Target Study Day	Study Day Range	Visit number
Screening (Visit 1)	-14 to -7	N/A	< 2
Screening (Visit 2)	-7 to -1	N/A	2 - < 3
Randomisation (Visit 3)	1	1	N/A
Visits 4 - 9	Refer to Table 1		

If multiple assessments are recorded within a single analysis visit window, the rules described in section 3.3.2 will be applied.

3.3.2.2 12-lead resting digital and safety electrocardiogram

The 12-lead digital ECG will be taken from visit 1 onwards. The analysis visit windows for visits 1 to 3 will be assigned based on the visit label and number for these data as described in Table 3.

For assessments made by the investigator used to confirm study inclusion criterion, the 'baseline' values available were those collected at screening (Visit 1). For analysis of this timepoint, the mean of all available triplicate measurements will be taken, as described above. Otherwise, individual assessments can be included as part of a triplicate if they were recorded on the same day and within 60 minutes of one another. If more than 3 individual measurements are available, the latest 3 values will be averaged for analysis. If only 1 or 2 individual measurements are available, the average of these will be taken.

3.3.2.3 12-lead resting digital electrocardiogram - extractions from Holter recordings

The purpose of this section is to define analysis time windows for Visit 3 and Visit 6 for the 12-lead resting digital ECGs derived from extractions from Holter recordings. Acceptable time windows for the target times defined in the CSP are presented in Table 4 below.

If multiple assessments occur in the same window for post-dose times as shown in Table 4, the mean of the triplicate that is closest to the target time within the respective time window will be used as the analysis value for the given timepoint.

Table 4 Schedule of 12-lead resting digital ECG extracted from digital Holter recording

Visit	Analysis Target Time	Time Interval for the Study Time Window
Visit 3 and 6	60 minutes pre-dose	120 to <0 min pre-dose
	20 minutes post-dose	0 to <45 min post-dose
	60 minutes post-dose	45 to <75 min post-dose
	4 hours post-dose	150 to 300 min post-dose

Note: ECG +60 min post study intervention dosing must be done prior to Spirometry post study intervention dosing.

3.3.2.4 Continuous digital 12-lead Holter electrocardiogram recordings

Holter hook-up procedures should be completed 1 day prior to scheduled Visits 3 and 6 at approximately the same time within the following time window 13:00 (+/ 2 hr) for both visits. The Holter monitor will be removed from the study participant at Visit 3 and 6 following collection of ECG recordings at 4 hr post investigational product (IP) dose

(maximum duration could be up to 30 hours if the Holter monitor is not stopped manually 4 hours post IP dose).

Because the Holter recordings should begin 1 day prior to visits 3 and 6, the study day range as specified is expected to begin 1 day earlier than defined in Table 1.

Specific analysis time periods for comparison are described in section 4.2.5.1.

4 STATISTICAL ANALYSIS

4.1 Study Population

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

4.1.1 Participant Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Participant disposition will be summarised using the enrolled analysis set according to treatment actually received.

The number and percentage (if applicable) of participants will be presented by the following categories:

- Screened
- Screen failures (and reason)
- Not randomised and not screen failed
- Randomised
- Randomised but not treated
- Started treatment
- Completed the 12-week treatment period
- Discontinued during the 12-week treatment period (and reason)
- Completed the 12-week visit
- Completed the 12-week visit but did not complete 12-week treatment period

- Assigned 52 weeks of treatment
- Assigned 52 weeks of treatment and started treatment
- Assigned 52 weeks of treatment and completed 52 weeks of treatment
- Assigned 52 weeks of treatment and discontinued
- Assigned 52 weeks of treatment and discontinued before completing 12 weeks of treatment (and reason)
- Assigned 52 weeks of treatment and discontinued after completing 12 weeks of treatment (and reason)
- Completed the 52-week visit
- Completed the 52-week visit but did not complete the 52-week extension treatment period.

Disposition summaries will also be produced for the stratification categories at randomisation. Randomisation is stratified by region (Americas, Europe) and COPD disease severity (percent predicted $FEV_1 \geq 50\%$, percent predicted $FEV_1 < 50\%$). Actual COPD severity at baseline as recorded in the spirometry data is determined by the maximum of the percent predicted FEV_1 values collected at 30 minutes post-bronchodilator and 60 minutes post-bronchodilator at visit 2.

4.1.1.2 Presentation

A disposition table for all enrolled participants will be provided. Disposition by region and actual COPD severity at baseline (as recorded in spirometry data) will also be provided. Discontinued participants and participants completing the study will also be listed separately.

Participant recruitment by country, site and region will be summarised by actual treatment received and overall.

The number of participants randomised will be summarised for 12-week safety set and 52-week safety set respectively, by region, country, site, COPD severity at baseline, and treatment, based on records in (a) the Interactive Response Technology (IRT), and (b) the eCRF and spirometry data. Participants whose IRT stratification group does not match the group as recorded in eCRF and spirometry data will be listed.

Disposition due to global/country situation will be provided. The following will be summarised: participants who completed treatment; and participants who withdrew from

study due to global country situation. This summary will be provided by treatment received and overall.

Summary of global/country study disruptions will be provided: participants with at least one global/country situation disruption; participants with visit impacted; participants with study drug impacted; and participants who withdrew from study due to global/country situation. This summary will be provided by treatment received and overall.

Listings for global/country situation disruptions will also be provided.

4.1.2 Analysis Populations

4.1.2.1 Definitions and Derivations

The definitions for the analysis populations are described in section 3.1. The number of participants included or excluded (and reason) from an analysis population within each treatment group will be presented by the 12-week safety analysis set and the 52-week safety analysis set. Participants will be excluded from both populations if they did not receive study intervention.

4.1.2.2 Presentation

A summary of all analysis populations will be provided. All participants enrolled with their inclusion/exclusion status and the reason for exclusion if they were excluded will be listed.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

The study Protocol Deviations Plan outlines the management of important protocol deviations (IPDs) and includes the specific categories of IPDs in this trial. Any PDs not defined as important will not be reported or discussed in the CSR.

4.1.3.2 Presentation

IPDs will be summarised for participants for each safety analysis set.

The number and percentage of participants for each important PD will be presented by treatment received for all participants randomised. Participants with IPDs will also be listed.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographic variables summarised will include the following:

- Age (years) as defined by age at Screening derived from the date of birth field on the demographics page of the eCRF

- Age group (≥40 to <65, ≥65 to ≤80) as defined by age at Screening derived from the date of birth field on the demographics page of the eCRF
- Sex (Male, Female) as collected on the demographics page of the eCRF
- Race (Black or African American/Native Hawaiian or other Pacific Islander/American Indian or Alaska Native/Asian/White/Other) as collected on the demographics page of the eCRF
- Ethnic group
- Country.

4.1.4.2 Presentation

Demographics will be summarised for participants for each safety analysis set.

Demographic characteristics variables will be summarised by treatment received and in total. No formal tests of statistical significance will be performed on the demographic and baseline data. Demographic data will also be listed.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline characteristic variables will include the following:

- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m^2)

where BMI = Weight (kg)/[[Height (m)]^2].

Number of pack years smoked = (number of cigarettes per day / 20) * number of years smoked.

4.1.5.2 Presentation

Baseline characteristics will be summarised for participants for each safety analysis set. These summaries will be performed by treatment received and overall.

Number of participants (n), mean, standard deviation, median, minimum and maximum will be reported.

A separate listing providing a display of height, weight and BMI will also be provided.

The number and percentage of participants with current nicotine use and former nicotine use will be reported, and the number of pack-years will be summarised. Smoking history will also be listed separately.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Bronchodilator Responsiveness to Albuterol

Bronchodilator responsiveness will be a comparison of the average best FEV_1 effort obtained at approximately 60 to 30-minutes pre-bronchodilator to the best FEV_1 effort obtained at 30 minutes (or up to 60 minutes, if repeated) post-bronchodilator following administration of albuterol at Visit 2.

Disease background characteristic variables will be summarised and will include the following at baseline, pre-bronchodilator at visit 2, and 30 min and 60 min post-bronchodilator at visit 2:

- FEV_1 (L)
- Percent predicted FEV_1 (%)
- FVC (L)
- FEV_1/FVC;

and will include the following at 30 min and 60 min post-bronchodilator at visit 2:

- Bronchodilator responsiveness (L)
- Bronchodilator responsiveness (%).

4.1.6.2 Presentation

The above disease characteristics will be summarised for each safety analysis set.

The n, mean, SD, minimum, median, maximum will be reported by treatment received.

Screening lung function as well as variables contributing to Bronchodilator Responsiveness to Albuterol at Visit 2 will be listed.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical and surgical history will be collected at Visit 1.

Medical history related to COPD diagnosis will be recorded on a separate disease history eCRF page. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 26.1 (or a later version if updated during the study)].

Variables summarised from the COPD history eCRF page will include:

- Was COPD diagnosed?
- COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification

GOLD Classification Disease Severity

GOLD classification of disease severity is a field on the COPD History Details page. COPD can be categorised into one of five categories according to this scale:

- At risk (0)
- Mild (1)
- Moderate (2)
- Severe (3)
- Very Severe (4).

4.1.7.2 Presentation

The number and percentage of participants with any medical history will be summarised by treatment received and in total for each safety analysis set. The number and percentage of participants with at least one medical history record within each primary system organ class (SOC) and preferred term (PT) will be presented. The summary will be sorted by international order for SOC and alphabetically by PT. A participant can have one or more PTs reported under a given SOC but will be reported once per PT and SOC. Surgical history/procedures will be presented similarly and separately from medical history.

COPD history at screening will be presented separately and summarised by treatment received and in total for the 12 and 52-week analysis sets. This will include the frequency and percentage of COPD diagnosed (yes/no), and the frequency and percentage of participants in each COPD GOLD classification category.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Coding: Verbatim medication/treatment terms will be coded and assigned a PT and an Anatomic Therapy Class (ATC) term using the latest version of the World Health Organisation Drug Dictionary (WHO-DD 092023) at the time of clinical data lock.

Multiple ATC assignments: If there are multiple ATC codes assigned to the same concomitant medication, the "primary" one based on medical evaluations will be used.

Prior medication is any medication taken and stopped prior to the start of study treatment.

Concomitant medication is any medication either with a start date after the first dose date of study treatment, or with a start date before, and either has a stop date on or after the first dose date of study treatment, or is ongoing. Medications started after the last dosing date of study treatment will not be considered as concomitant.

COPD Maintenance Medications

COPD maintenance medications are defined as ICS/LABA, LAMA/LABA, SABA/SAMA, or ICS/LAMA/LABA inhaled maintenance therapies for the management of their COPD for at least 6 weeks prior to Screening. Roflumilast, Xanthine derivatives and other COPD maintenance medication categories will also be reported. These are medications which are indicated on the eCRF as "COPD" or "COPD stable maintenance dose" on the "Therapy reason" field of the Medications of Interest page.

COPD Related Medications

COPD related medications will be defined as medications which are indicated on the eCRF as "COPD", "COPD exacerbation per protocol", "COPD stable maintenance dose", "Titration, due to change of COPD control", or "Worsening of COPD, without exacerbation" on the "Therapy reason" field of the Medications of Interest page.

Disallowed Medications

Disallowed medications will be identified by medical review prior to clinical data lock.

4.1.8.2 Presentation

The following summaries will be provided for each safety analysis set: Prior medications will be summarised by actual treatment received. Medications taken during screening period will be presented separately as COPD related and non-COPD related by actual treatment received. Concomitant medications will be presented separately as COPD related and non-COPD related by actual treatment received. Disallowed medication use will also be summarised by actual treatment received.

Listings will be provided for prior medications, medications taken during screening period, and concomitant medications, respectively. For medications that are taken during screening period or concomitant, separate listings will be provided for those that are COPD related and non-COPD related.

COPD maintenance medications at screening will be summarised by reporting the number and percentage by maintenance medication group defined in 4.1.8.1. The number and percentage of participants reporting such medications will be reported by actual treatment received. A listing of COPD maintenance medications will also be provided.

4.1.9 Study Treatment Compliance

4.1.9.1 Definitions and Derivations

Percent compliance with study treatment is defined as:

$$\text{Compliance (\%)} = 100 \times \frac{\text{\# of IP inhalations taken}}{\text{Expected \# of IP inhalations}}$$

The expected number of IP inhalations will be based on the participant's actual duration in the study – i.e. if they discontinue early, the expected number of days on treatment will be adjusted accordingly. Drug interruptions (e.g. due to an AE) will not be included in the participant's actual duration. The actual total number of inhalations will be derived using the Drug Accountability eCRF page.

The dosing schedule is 2 inhalations BID, that is, 4 inhalations per day during the treatment period. The expected number of inhalations for a visit day which is the last date of treatment will be 2, and the expected number of inhalations for the last date of treatment which is not a visit day will be 4 when an evening dose is taken but will be 2 otherwise. If the time of the last dose is not available, the expected number of inhalations will be 2. The expected number of inhalations on dates prior to the last date of treatment will be 4.

Out of the 130 inhalations available per dispensed device, 10 will be used for MDI maintenance; initial device priming requires 4 inhalations to be used, and 2 inhalations will be used for maintenance at each of 3 weekly maintenance cleaning cycles (at the beginning of weeks 2, 3 and 4 of treatment). Therefore, 120 inhalations per dispensed device will be available for treating the participant for each 4-week period. The expected number of inhalations will be derived from the participant's treatment start and end dates, and Exposure as Collected eCRF page.

4.1.9.2 Presentation

Study treatment compliance percentage will be summarised by treatment received for each safety analysis set. The number of participants and percentage in each compliance

percentage category (0 - ≤20%, >20 - ≤50%, >50 - ≤80%, >80 - ≤ 100%, >100 - ≤120%, and >120%) will be reported by treatment received and overall.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, and other endpoints including supportive analyses.

Table 5 Endpoint Analysis

Statistical category	Endpoint	Population	Details in section
Objective 1: To assess the safety and tolerability of BGF MDI HFO as compared to BGF MDI HFA over 12 to 52 weeks in participants with moderate to very severe COPD.			
Primary	AEs (including SAEs, DAEs, AEOSIs, non-serious AEs)	12-Week Safety Analysis Set & 52-Week Safety Analysis Set	4.2.2
Primary	Digital 12-lead Holter ECG	12-Week Safety Analysis Set	4.2.5
Primary	12-lead ECG	12-Week Safety Analysis Set & 52-Week Safety Analysis Set	4.2.4
Primary	Clinical laboratory testing	12-Week Safety Analysis Set & 52-Week Safety Analysis Set	4.2.3
Primary	Vital signs	12-Week Safety Analysis Set & 52-Week Safety Analysis Set	4.2.6
Exploratory	Change from pre-dose value in FEV_1 at 5, 15, 30, and 60 min post-dose	12-Week Safety Analysis Set & 52-Week Safety Analysis Set	4.2.7
Objective 2: To explore the effect of BGF MDI HFO as compared to BGF MDI HFA over 12 to 52 weeks on respiratory health status.			
Exploratory	Change from baseline CAT at 12 and 52 weeks	12-Week Safety Analysis Set & 52-Week Safety Analysis Set	4.2.8

4.2.1 Exposure

4.2.1.1 Definitions and Derivations

Participant's exposure to IP is determined by the duration of time (days) for which the doses were administered:

Exposure = End date of IP – Date of first dose of IP + 1

Exposure is also defined for the first 12 weeks of treatment:

Exposure (0-12 weeks) = min(End date of IP, Week 12 visit) – Date of first dose of IP + 1

The total person-years of exposure for a treatment group is defined as the total exposure days in the study (or in 0-12 Weeks period) summed over all participants in the treatment group, divided by 365.25.

4.2.1.2 Presentation

The number of days of exposure to study treatment will be summarised for each treatment received. Summary statistics will also be provided for the cumulative duration of exposure, where the number and percentage of participants treated for 0-12 weeks and for 0-52 weeks and corresponding person-years will be provided for the following periods of time: at least 1 day, ≥4 weeks, ≥8 weeks, 12 weeks, ≥26 weeks, ≥40 weeks, and 52 weeks. The total person-years of exposure will also be presented by treatment received.

Administration of IP listing will be provided. A separate listing will also be provided for the various batch numbers of IP each participant received.

4.2.2 Adverse Events

4.2.2.1 Definitions and Derivations

Adverse Events

AEs include both serious and non-serious

Adverse Events

AEs 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 even if no study intervention has been administered.

AEs will be collected from randomisation and throughout the treatment period and including the follow-up period. All SAEs will be recorded from the time of signing ICF.

AEs will be categorised for analysis according to their onset date into the following study periods:

- AEs occurring during screening/run-in period: date of Visit 1 ≤ AE onset date < date of first dose of IP after randomisation (SAEs only).
- AEs occurring during treatment period: date of first dose of IP after randomisation ≤ AE onset date ≤ date of last dose of IP + 1 day.

- AEs occurring during post-treatment period (for participants still being followed up then): date of last dose of IP + 1 day < AE onset date ≤ study completion or study withdrawal date.

For determination of inclusion of an AE in the treatment period, if the AE start date is partial/missing, then:

- If AE start date is completely missing, then the AE is considered to have occurred during the treatment period.

- If both AE start month and day are missing and AE start year is the same or after the first dose year, then the AE is considered to have occurred during the treatment period.

- If AE start day is missing and AE start year and month are the same or after the first dose year and month, then the AE is considered to have occurred during the treatment period.

For EAIR related calculations, if the AE start date is partial/missing, then:

- If day is missing, impute the 1st of the month unless month is the same as month of first dose of study drug, then impute first dose date.

- If day and month are missing, impute 1st January unless year is the same as the first dose of study drug, then impute first dose date.

- If date is completely missing, impute first dose date unless the end date suggests it could have started prior to this, in which case impute 1st January of the same year as the end date.

- When imputing a start date, ensure that the new imputed date is sensible, i.e., is prior to the end date of the AE or medication.

Missing/incomplete (partial) AE start and end dates will not be imputed for data listings.

Serious Adverse Events

A SAE is an AE occurring during any study phase that fulfils one or more of the following criteria:

- Results in deathIs immediately life-threatening

- Requires in-participant hospitalisation 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

SAEs will be identified on the Adverse Events eCRF page.

Adverse Events of Special Interest

AEOSIs in this study are respiratory events such as dysphonia, cough, dyspnea, wheezing, paradoxical bronchospasm, bronchospasm and COPD exacerbation. AEOSIs will be identified on the Adverse Events eCRF. A list of PTs covering listed respiratory events will be used for the purposes of defining AEOSI.

Paradoxical Bronchospasms

Paradoxical bronchospasm (PB) is defined as a reduction in FEV_1 of >15% from baseline (i.e., the FEV_1 value obtained within 30 minutes prior to study intervention administration on that same day) that occurs shortly after dosing with associated symptoms of wheezing, shortness of breath, or cough. These symptoms will also have to be identified on the eCRF and identified as occurring within 15 minutes post IP dose. A list of PTs covering listed respiratory events will be used for the purposes of defining PB. Cases of PB will be confirmed by medical review.

Adverse Event Exposure-Adjusted Incidence Rate

The adverse event exposure-adjusted incidence rate (EAIR) is defined as the number of participants with at least one event occurring during a specified period (0-12 weeks, 0-52 weeks) divided by the total number of years at risk for the event summed over all participants in the period. The number of years at risk is calculated as the number of days since the first dose of IP to the last date the participant is followed-up in the specified period, or the first occurrence of the event, whichever is earlier, divided by 365.25. EAIR per 100 subject years, calculated as EAIR * 100, will be presented.

The difference in EAIR between treatment groups (HFO-HFA) and 95% CI for the difference will be estimated, using the Miettinen and Nurminen method (Miettinen and Nurminen 1985). Details of the CI calculations are included in Appendix section 7.1. The difference between EAIR per 100 subject years and the corresponding CI will be presented, calculated as the original EAIR difference and CI limits multiplied by 100.

This approach will be used for computing the difference in EAIRs for Paradoxical Bronchospasms, any AEOSI, any AE leading to discontinuation of IP, and any SAE. EAIR will also be calculated for the overall summary table of AEs.

4.2.2.2 Presentation

All AEs during the treatment period will be reported whether or not they are considered to be related to treatment. All available data in the study population should be accounted for in the evaluation, subject to the rules outlined in section 3.2.

The number and percentage of participants with at least one of the following AEs, and the number of events and EAIRs will be summarised using the 12 and 52-week safety analysis sets during the treatment period:

- Any AE
- Any SAE
- Any SAE with outcome death
- Any AE leading to discontinuation of IP
- Any AEOSI
- Any AE possibly related to IP
- Any SAE possibly related to IP.

The following is a list of summary tabulations that will be prepared for the AE data during the treatment period by treatment received using the 12 and 52-week safety analysis sets:

- AEs by SOC and PT
- AEs by PT, sorted by decreasing frequency on PT
- Most common AEs (occurring in ≥ 2% of participants in either treatment group) by PT sorted by decreasing frequency in the HFO group
- AEs by SOC and PT and maximum intensity
- Severe AEs by SOC and PT
- AEs possibly related to IP
- AEOSIs by PT

- AEOSIs by PT and maximum intensity
- AEOSIs by timing relative to the IP inhalation
- Paradoxical bronchospasm
- SAEs with outcome of death, by SOC and PT
- SAEs by SOC and PT
- SAEs possibly related to IP
- SAEs by PT, sorted by decreasing frequency on PT
- Serious AEOSIs sorted by decreasing frequency on PT
- AEs leading to discontinuation of IP, by SOC and PT
- Non-serious AEs occurring in greater than 5% of participants, by SOC and PT .

Exposure-adjusted incidence rates (EAIRs), the rate difference (HFO - HFA) and 95% CI will be presented for

- AEOSIs by PT
- SAEs by SOC and PT
- AEs leading to discontinuation of IP, by SOC and PT
- PB

EAIRs will also be presented for the overall summary of AEs.

In addition, the following summaries will be prepared for the post-treatment period by treatment received:

- AEs by SOC and PT (participant count and event count)
- SAEs by SOC and PT (participant count and event count).

All AEs collected from randomisation and all SAEs collected from ICF signature will be included in a listing. SAEs for enrolled but not randomised participants and for participants who were not exposed to treatment will also be listed. Reported overdoses will be listed.

Tables will present key participant information for all AEs leading to discontinuation of investigational product, SAEs with outcome of death and SAEs.

4.2.2.3 Subgroup Analyses

Subgroup analysis will be provided for the number and percentage of participants with AEs by SOC and PT during the treatment period by treatment received for each safety analysis set for the following categorical variables: age group, sex, and race, as specified in Section 4.1.4.

If not stated otherwise, the subgroup analysis will not be performed for a sub-population if any treatment group consists of less than 30 participants within that sub-population.

4.2.3 Clinical Laboratory Assessments

4.2.3.1 Definitions and Derivations

The clinical chemistry and haematology will be performed at a central laboratory, except for urine human chorionic gonadotropin (hCG) test which will be performed at study site.

All clinical laboratory tests will be obtained at Visit 1 and at Visit 3, Visit 6, and Visit 9, End-of-treatment/Withdrawal Visit, and any unscheduled visit.

Clinical haematology parameters measured include: haemoglobin, white blood cell count with differential, and platelet count.

Clinical chemistry parameters measured include: creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, glucose, potassium, and sodium.

Table 6 Laboratory Variables

Haematology/Hemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Hemoglobin	Creatinine
B-Leukocyte count	Bilirubin, total
B-Leukocyte differential count (absolute count)	Alkaline phosphatase
B-Platelet count	Aspartate transaminase
S-β-hCG (Pregnancy test) at Visit 1	Alanine transaminase
U-β-hCG pregnancy for all visits except Visit 1	Potassium
S-FSH[a] at Visit 1 only	Sodium
eGFR[b]	Glucose
Troponin[c]	

a. Serum FSH test is only required for eligibility check. FSH is tested at Visit 1 for women <50 years of age with amenorrhea for 12 months without an alternative medical cause.
b. eGFR estimated by the CKD-EPI formula for participants 18 to 80 years of age to be calculated at Visit 1, 3, 6, 9 and Withdrawal Visit.
c. Troponin use only as a Baseline measurement in the study at Visit 3 prior to study intervention administration. Post randomisation troponin should be checked according to the Investigator's decision and only when clinically indicated for potential Adverse Events diagnosis/reporting.

In all analyses of continuous laboratory variables, any value recorded as below the lower limit of quantitation (LLOQ) will be set to LLOQ and included in the analysis. Any value recorded as above the upper limit of quantitation (ULOQ) will be set to ULOQ and included in the analysis. In listings, such values will be displayed as collected.

Absolute values will be compared to the relevant normal reference range, and classified as low (below range), normal (within range or on the limits) or high (above range). All values falling outside the normal reference ranges will be flagged accordingly and used for summaries of abnormalities and shift tables. An exception is eGFR, where abnormality is based on change from baseline – eGFR abnormalities are those with decrease from baseline ≥ 1 in CTCAE grade and a decrease of ≥ 20% compared to baseline value.

Visit windows defined in section 3.3.2 are not used when determining the minimum, maximum or last value. Minimum, maximum and last values calculated across all visits in the relevant study period will use all available values, including those from unscheduled and repeat visits.

4.2.3.2 Presentation

For each safety analysis set the following analysis will be performed:

Summary statistics (n, mean, SD, minimum, Q1, median, Q3, maximum) for absolute values and change from baseline values will be tabulated by treatment received and scheduled assessment time. These summaries will be prepared for baseline, each scheduled post-baseline visit and end of treatment visit. End of treatment visit is defined as the last non-missing post randomisation assessment available. Data from unscheduled visits will not be used for the by-visit summaries, but both scheduled-visit data and unscheduled-visit data are candidates for the end-of-treatment summary. Data from both scheduled and unscheduled visits will be listed. No hypothesis tests will be performed.

During the treatment period, participants with absolute values outside relevant normal reference ranges will be flagged as abnormal and summarised. Key participant information for chemistry and haematology abnormalities will also be provided.

Shift tables will be provided by treatment received for baseline reference range category vs maximum observation category and vs. minimum observation category. Percentage of participants in each reference range category combination will be calculated by treatment received. A shift table for kidney function (eGFR, based on Common Terminology Criteria for Adverse Events (CTCAE) v5 laboratory test criteria only for eGFR values from Grade 0 to 5) will also be provided.

A listing of individual laboratory measurements will be provided. A separate listing for pregnancy test will be provided.

4.2.4 Electrocardiogram

4.2.4.1 Definitions and Derivations

ECG data comes from the following different sources, at the timepoints specified in the CSP as follows:

- Investigator's bedside evaluations – referred to as '12-lead resting safety ECG overall evaluation' – collected at visit 1 (screening), visit 4, visit 5, visit 9 (for participants assigned to 52-weeks of treatment) and withdrawal.

- Clario's evaluations – referred to as '12-lead resting digital ECG overall evaluation' – collected at visit 1 (screening), visit 4, visit 5, visit 9 (for participants enrolled to 52-weeks of treatment), and withdrawal.

- Clario's evaluations – referred to as '12-lead resting digital ECG overall evaluation' – collected at 60 minutes pre-dose, 20 minutes post-dose, 60 minutes post-dose and 4 hours post-dose, on visits 3 and 6, from Holter extractions.

- ECG numeric variables – referred to as '12-lead resting digital ECG' – triplicate measurements collected at visit 1 (screening), visit 4, visit 5, visit 9 (for participants assigned to 52-weeks of treatment), and withdrawal.

- ECG numeric variables – referred to as '12-lead resting digital ECG' – triplicate measurements collected at 60 minutes pre-dose, 20 minutes post-dose, 60 minutes post-dose and 4 hours post-dose, on visits 3 and 6, from Holter extractions.

The ECG parameters to be assessed include HR, PR interval, QRS interval, RR-interval, QT interval, and QTcF interval. The analysis of 12-lead resting digital ECG will be based on the overread by a Clario cardiologist and verified digital ECG data. Baseline for the 12-lead resting digital ECGs is defined in section 3.3.1.

Overall ECG evaluation of the 12-lead resting safety (bedside) ECGs will be recorded by site investigators in the eCRF as "Normal", "Abnormal", and "Borderline" at visit 1 (screening), visit 4, visit 5, visit 9 (for participants assigned to 52-weeks of treatment), and withdrawal. These bedside assessments could be made at any time by the investigator outside of these scheduled visits if clinically indicated. Further, investigators will specify if the results are "not clinically significant" or "clinically significant".

12-lead resting digital ECG overall evaluation of "Normal" or "Abnormal" will also be made by a cardiologist at Clario. The final clinical significance assessment of a potential ECG abnormality will be made by the responsible investigator.

When more than one overall evaluation or clinical significance assessment is recorded for either the safety or digital ECGs, the worst will be reported of each (with "Abnormal" being the worst evaluation, and "Clinically significant" the worst assessment).

The below thresholds will be used for tabulating increases in QTcF values, with baseline as defined in section 3.3.1.

Table 7 Summary Thresholds for QTcF

Parameter	Baseline Criteria	Post-Baseline Criteria
QTcF value	>450 ms	>450 ms
	>480 ms	>480 ms
	>500 ms	>500 ms
QTcF change from baseline		>30 ms
		>60 ms
QTcF value and/or change from baseline		Value >480 ms and increase from baseline >60 ms
		Value >500 ms and increase from baseline >60 ms
		Value >500 ms or increase from baseline ≥60 ms (discontinuation criteria)

ms denotes milliseconds.

4.2.4.2 Presentation

For each safety analysis set the following analysis will be performed:

Summary statistics (n, mean, SD, minimum, Q1, median, Q3, maximum) of the absolute values and change from baseline for resting digital ECGs will be tabulated by treatment received and timepoint. These summaries will be prepared for baseline, each scheduled post-baseline visit and the withdrawal visit. For the baseline definition, refer to Section 3.3.1. For post-baseline visits, the mean of the triplicate measurements from each visit or timepoint will be taken for the summary. Data from unscheduled visits will not be used for the by-visit summaries. Data from both scheduled and unscheduled visits will be listed. No hypothesis tests will be performed.

A frequency table of QTcF values at baseline, post-baseline visits and post-dose overall (at any time), and changes from baseline, using pre-specified thresholds (Table 7) will be produced by treatment received.

A shift table will be produced as follows: the participant's baseline 12-lead resting digital ECG evaluation will be cross-tabulated by the evaluation at each post-dose visit, by treatment received and overall. The 12-lead resting safety ECG will also be cross-tabulated with screening (visit 1) evaluations.

Key participant information for ECG abnormalities will also be provided.

Individual resting digital ECG data will also be provided in a listing, including each individual triplicate measurement and the mean used for summaries. Separate listings will be provided for 12-lead resting digital ECG overall evaluations, and for 12-lead resting safety ECG overall evaluations for each visit, both including each triplicate measurement and the overall selected evaluation.

Assessments that are not evaluable will be excluded in analysis but included in listings.

4.2.5 Digital 12-lead Holter Electrocardiogram

4.2.5.1 Definitions and Derivations

Continuous Digital 12-lead Holter ECG will be performed at Visit 3 and Visit 6. The ECG arrhythmia monitoring will take place over approximately 24 hours, and Holter will be connected the day prior to Visit 3 and Visit 6 to allow for 24 hours of monitoring.

Holter recording data will be hourly and anchored to IP administration time except for the first record, which will start at the actual hook-up time. For example, if a Holter recording begins on day -1 at 13:10, and IP administration takes place on day 1 at 08:30, baseline 1 (see section 3.3.1 for definition) would use the records covering 13:10 – 13:29, 13:30 – 14:29, 14:30 – 15:29, and 15:30 – 16:29 on day -1.

Holter recordings may be interrupted or stopped and started again hours later. For the purpose of this analysis, only continuous recordings that were uninterrupted and had an analysis duration of at least 12 hours will be used. If no IP dose was taken on the visit in question, the Holter recording will not be included in summary tables, but will be included in by-visit listings.

Evaluations (“Normal”, “Abnormal”, or “Unable to evaluate”) will be provided for each recording period, but only continuous recordings that were uninterrupted and had an analysis duration of at least 12 hours will be used (including both pre and post-dose periods. If more than one evaluation is recorded, the worst will be reported.

Change from baseline in rhythm parameters will be evaluated, where baseline is defined as specified in 3.3.1, for analysis time periods as follows:

- Daytime only comparison: Baseline 1 compared with Visit 3 60 minutes post-dose, 4 hours post-dose, Visit 6 60 minutes post-dose, 4 hours post-dose
- Day and nighttime comparison: Baseline 2 compared with the period from start of recording on Visit 6 until next IP administration.

Continuous parameters measured hourly will be summarised by the average value per hour during the analysis period, or maximum or minimum per analysis period.

Some parameters are only recorded per visit (not hourly), and will not be presented using the analysis time periods defined above. Therefore, there will be no baseline vs post-baseline comparison. For these parameters, the original measurements will be summarised in analysis, except for atrial fibrillation burden values of "<1%", where 0.5% will be imputed.

4.2.5.2 Presentation

For the 12-week safety analysis set only, the following analyses will be performed for the daytime and day and nighttime comparisons defined in section 4.2.5.1, or by visit:

Summary statistics (n, mean, SD, minimum, Q1, median, Q3, maximum) of the absolute values and change from baseline for rhythm parameters will be tabulated by treatment received and analysis period (for parameters recorded hourly) or by visit. Holter analysis duration will also be summarised by treatment received and by Holter recording period (Visit 3 and 6). No hypothesis tests will be performed.

The number and percentage of participants with at least one occurrence of ventricular singles, supraventricular singles, supraventricular couplets, supraventricular runs, and ventricular couplets will be summarised by treatment received and analysis period. The number and percentage of participants with ventricular runs of 3-5, 6-10 or >10 beats will also be summarised.

The number and percentage of participants with at least one occurrence of atrial fibrillation or atrial flutter, 2:1 AV block, AV block 2 type I (Mobitz type I), AV block 2 type 2 (Mobitz type II), AV block 3 (complete AV block) , and high grade AV block will be summarised by treatment received and Holter recording period (Visit 3 and 6).

Changes from baseline in single ventricular premature contractions (VPCs), including increases or decreases of 0 - <60, 60 to <120 and ≥120 will be summarised by treatment received. The number and percentage of participants with ≥30 single VPCs in one hour during the specified analysis periods will also be summarised.

Maximum heart rate (>180, 160 - ≤180, 140 - ≤160, 120 - ≤140, 100 - ≤ 120, ≤100) and minimum heart rate (>60, >50 - ≤60, >40 - ≤50, ≤40) will be summarised for each analysis period by treatment received.

The overall evaluations by Clario per Holter recording period will be summarised for Visit 3 and Visit 6 by treatment received in a frequency table, and also listed.

Arrhythmia analysis results and arrhythmia events will be summarised by visit, and also listed. Analysis duration will be summarised by visit.

Listings of individual digital 12-lead Holter ECG data and arrhythmia findings will be provided. A separate listing will also be provided for digital 12-lead Holter ECG overall evaluations per visit.

4.2.6 Vital Signs

4.2.6.1 Definitions and Derivations

Vital signs will be measured according to the schedule and variable specifications described in the CSP. Changes from baseline will be evaluated, where baseline is defined as specified in section 3.3.1.

Absolute values and changes from baseline will be compared to the relevant reference range specified in Table 8, and classified as low (below range), normal (within range or on the limits) or high (above range). All values falling outside the reference range will be flagged as abnormal.

Table 8 Vital Signs Reference Ranges

Parameter	Standard Units	Lower Limit	Upper Limit	Changes from Baseline Criteria
Diastolic BP (sitting)	mmHg	60	100	±15
Systolic BP (sitting)	mmHg	90	160	±30
Pulse rate (sitting)	beats/min	50	100	±20
Weight	kg	40	150	

4.2.6.2 Presentation

For each safety analysis set the following analysis will be performed:

Summary statistics (n, mean, SD, minimum, Q1, median, Q3, maximum) of the absolute value and change from baseline for vital signs will be tabulated by treatment received and visit. These summaries will be prepared for baseline, each scheduled post-baseline visit and end of treatment visit. End of treatment visit is defined as the last non-missing post randomisation assessment available. Data from unscheduled visits will not be used for the by-visit summaries, but both scheduled-visit data and unscheduled-visit data are candidates

for the end-of-treatment summary. Data from both scheduled and unscheduled visits will be listed. No hypothesis tests will be performed.

During the treatment period, participants with absolute values or change from baseline values outside vital signs reference ranges will be flagged as abnormal and summarised. Key participant information for vital sign abnormalities will also be provided.

Shift tables will be provided by treatment received for baseline reference range category vs maximum and vs minimum observation category. Percentage of participants in each reference range category combination will be calculated by treatment received.

4.2.7 Spirometry

4.2.7.1 Definitions and Derivations

Forced expiratory spirometry manoeuvres will be assessed to derive the following parameters.

- FEV_1 is the volume of air exhaled under forced conditions in the first second,
- FVC is the determination of the vital capacity from a maximally forced expiratory effort
- FEV_1/FVC ratio.

For FEV_1 and FVC the percent predicted value is directly available as well.

FEV_1 (L and percent predicted) will be analysed at baseline, Week 4, Week 8, Week 12 as well as Weeks 26, 40 and 52 if applicable. Post IP inhalation values at 5, 15, 30, 60 minutes will be compared to the pre-dose value obtained on the same day, and will be referred to as “change from pre-dose”.

Only data where Pulmonary Test Number is 0 (best effort) and the effort time occurs within an analysis time window (section 3.3.2.1) will be analysed.

Each test will have a corresponding Quality Grade:

1 = acceptable

2 = borderline

3 = unacceptable

Only data where Quality Grade is 1 or 2 will be included in baseline or treatment period spirometry calculations.

4.2.7.2 Presentation

For each safety analysis set the following analysis will be performed:

Absolute values and change from pre-dose in FEV_1 (L and percent predicted) will be summarised by analysis visit, time point, and treatment received.

Line plots of mean FEV_1 +/- standard error (L) by treatment received will be displayed graphically at each time point (30-min pre-dose & 5 min, 15 min, 30 min, 60 min post-dose) for each visit. Each line plot for each visit will appear on a separate page. Windows defined in section 3.3.2 will be applied in determining analysis values in each case.

A listing of all collected spirometry assessments will be provided.

4.2.8 COPD Assessment Total Score

4.2.8.1 Definitions and Derivations

CAT Total Score

The CAT is an 8-item Patient Reported Outcome developed to measure the overall impact of COPD on health status (Jones et al 2009). The CAT total score is the sum of item responses. If any of the individual items from the CAT score are missing the CAT total score is set to missing. Scores range from 0-40 with higher scores indicative of greater COPD impact on health status. Participants will complete the CAT at Visit 1, Visit 6, Visit 9, and the Withdrawal Visit.

4.2.8.2 Presentation

For each safety analysis set the following analysis will be performed:

The CAT total score at baseline and each post-baseline visit will be summarised. Change from baseline will also be summarised for each post-baseline time point by treatment received.

A listing for the COPD CAT assessment will also be provided.

5 INTERIM ANALYSIS

There is no interim analysis for this study.

6 REFERENCES

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Laud, P., ratesci-sas (Confidence intervals and tests for comparison of rates). Github repository [Internet]. 22 Dec 2023 [cited 2024 Jan 11; downloaded 2024 Jan 11]. Available from: https://github.com/PeteLaud/ratesci-sas.

7 APPENDIX

7.1 Exposure-Adjusted Incidence Rate and Confidence Interval Derivation

The below applies to both 12-week and 52-week reporting:

Step 1: Compute the total exposure time in years for each participant.

For participants who had the event in question, exposure time in years will be computed as:

(first event date - treatment start date + 1)/365.25

For participants who did not have the event in question, exposure time in years will be computed as exposure duration in days (see section 4.2.1.1) divided by 365.25.

Step 2: Sum the total exposure time in years for all participants by treatment group. This is the total person-years of exposure for a treatment group defined in section 4.2.1.1.

Step 3: Calculate the number of participants who had the event in each treatment group.

Step 4: Create a SAS dataset *dt* with variables E1 N1 E0 N0 (must be the exact same names listed here), where E1 is the number of participants with event in group 1, N1 is total exposure time in group 1, E0 is the number of participants with event in group 2, N0 is total exposure time in group 2.

Step 5: Run SAS macro SCORECI (Laud 2023) as below.

%scoreci(ds = dt, distrib = poi, stratify = FALSE, skew = FALSE);

Note that ‘poi’ must be all lower case, and ‘FALSE’ must be all upper case.

Step 6: In the output, the estimated EAIR difference is under ‘TRTDIFF’ column, and the corresponding lower and upper confidence limits are in the ‘L_BOUND’ and ‘U_BOUND’ columns. Multiply the values by 100 to obtain ‘per 100 subject years’ results.

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