STATISTICAL ANALYSIS PLAN

RPL554-CO-302

A PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ENSIFENTRINE OVER 24 WEEKS IN PATIENTS WITH MODERATE TO SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

[redacted]

VERSION NUMBER AND DATE: FINAL V1.0, 25JUL2022

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan FINAL V1.0 (Dated 25JUL2022) for Protocol RPL554-CO-302.

	Name	Signature	Date
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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	25JUL2022	Marco Sequi	Not Applicable – First Version

ABBREVIATIONS

AE	Adverse Event
ACS	Abnormal, Clinically Significant
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANCS	Abnormal, Not Clinically Significant
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Clinical Classification System
AUC_{0-t}	Area Under the Curve over t hours
BDI	Baseline Dyspnea Index
BDR	Blinded Data Review
BLQ	Below the Lower Limit of Quantitation
BMI	Body Mass Index
BPM	Beats Per Minute
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CV	Coefficient of Variation
DBL	Database Lock
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Echocardiogram
ENR	All Patients Enrolled
EOS	End of Study
EQ-5D-5L	EuroQol-5-Domain Questionnaire
E-RS^{TM}: COPD	Evaluating Respiratory Symptoms for COPD
ERT	eResearch Technology
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GGT	Gamma Glutamyltransferase
HRU	Healthcare Resource Utilization
IL	Interleukin
IV	Intravenous
LABA	Long-acting Beta 2 Agonist
LAMA	Long-acting Muscarinic Antagonist
LOCF	Last Observation Carried Forward
LOQ	Limit of Quantitation
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation

mITT	Modified Intent-to-Treat
mMRC	Modified Medical Research Council
MMRM	Mixed Model for Repeated Measures
PD	Protocol Deviation
PK	Pharmacokinetics
POPPK	Population Pharmacokinetics
PP	Per-Protocol
PT	Preferred Term
Qol	Quality of Life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RND	All Patients Randomized
SAP	Statistical Analysis Plan
SABA	Short-acting Beta 2 Agonist
SAE	Serious Adverse Event
SAF	Safety Analysis
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGRQ	St. George's Respiratory Questionnaire
SI	Standard International
SOC	System Organ Class
TDI	Transition Dyspnea Index
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data, including genotyping data for Protocol RPL554-CO-302. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.
This statistical analysis plan (SAP) is based on protocol version 5.0, dated 30th April 2021.

A separate analysis plan will be created which will include the details of the population PK (POPPK) analysis, as well as the design and modelling of the PK collection data. Only summarization of PK concentrations will be described in this SAP.

A separate pooled SAP will be created which will include the details of pooled analysis between RPL554-CO-301 and RPL554-CO-302.

There will also be a separate blinded data review (BDR) plan that will outline the process for identification and decision making on patient's exclusion from analysis sets and on major protocol deviations specified in the BDR plan. These will then be summarized in BDR report created for the data review outputs. This document will summarize each analysis set and reasons for the exclusion. In the BDR report protocol deviations (PDs) will also be outlined, specifying which patients were identified with each PD and whether these led to exclusion from the PP population. All analysis sets will be defined, and all possible PDs will be identified prior to unblinding. If there are any PDs which can only be identified post-unblinding (e.g. in PK or Biomarker data), an unblinded data review report will be created to detail these after database lock (DBL).

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the efficacy of ensifentrine on lung function compared to placebo over a 12-hour dosing interval in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

2.2. SECONDARY OBJECTIVES

- To evaluate the effect of ensifentrine on other lung function parameters.
- To evaluate the effect of ensifentrine on COPD symptoms.
- To evaluate the effect of ensifentrine on health-related quality of life.

2.3. OTHER OBJECTIVES

- To evaluate the effect of ensifentrine on moderate/severe COPD exacerbations.
- To evaluate the effect of ensifentrine on health utility and healthcare resource utilization (HRU).
- To characterize the pharmacokinetics of ensifentrine in patients with COPD.
- To evaluate the effect of ensifentrine on inflammatory biomarkers.

2.4. SAFETY OBJECTIVES

To evaluate the safety and tolerability of ensifentrine over 24 Weeks.

2.5. ESTIMANDS

The primary and secondary estimands to support regulatory decisions are described in Table 1.

Table 1: List of Estimands

Estimand	Definition	Attributes			
		Population	Variable/ Endpoint	Intercurrent event handling strategy	Population-level summary measure
Primary	The efficacy of ensifentrine on lung function compared to placebo over a 12-hour dosing interval in patients with moderate to severe COPD.	Patients with moderate to severe COPD aged 40-80 years (inclusive) that are in the modified intent-to-treat (mITT) population. See full list of inclusion and exclusion criteria in sections 5.1, 5.2 and 5.3 of study protocol.	Change from baseline forced expiratory volume in 1 second (FEV_1) to average FEV_1 area under the curve over 12 hours (AUC_{0-12h}) at Week 12.	Regardless of whether the patient discontinues treatment prematurely and regardless of major protocol deviation, as per the Treatment Policy strategy.	Estimated treatment difference at Week 12 of the double-blind period (and corresponding 95% confidence interval [CI]) from analysis of covariance (ANCOVA) analysis.
Secondary	To evaluate the effect of ensifentrine on other lung function parameters.	Patients with moderate to severe COPD aged 40-80 years (inclusive) that are in the mITT population. See full list of inclusion and exclusion criteria in sections 5.1, 5.2 and 5.3 of study protocol.	1. Change from baseline FEV_1 to average FEV_1 AUC_{0-4h} at Week 12 2. Change from baseline FEV_1 to peak FEV_1 at Week 12 3. Change from baseline FEV_1 to morning trough FEV_1 at Week 12	Regardless of whether the patient discontinues treatment prematurely and regardless of major protocol deviation, as per the Treatment Policy strategy.	Estimated treatment difference at Week 12 of the double-blind period (and corresponding 95% CI) from ANCOVA analysis.

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Secondary	To evaluate the effect of ensifentrine on COPD symptoms.	Patients with moderate to severe COPD aged 40-80 years (inclusive) that are in the mITT population. See full list of inclusion and exclusion criteria in sections 5.1, 5.2 and 5.3 of study protocol.	Change from baseline (i.e. mean over the last 7 days of run-in) to the mean weekly value at Week 24 in COPD symptoms, as measured by daily diary (Evaluating Respiratory Symptoms for COPD [E-RS^{TM}:COPD])	Regardless of whether the patient discontinues treatment prematurely and regardless of major protocol deviation, as per the Treatment Policy strategy.	Estimated treatment difference at the end of the double-blind period (and corresponding 95% CI) from ANCOVA analysis.
Secondary	To evaluate the effect of ensifentrine on health-related quality of life.	Patients with moderate to severe COPD aged 40-80 years (inclusive) that are in the mITT population. See full list of inclusion and exclusion criteria in sections 5.1, 5.2 and 5.3 of study protocol.	1. Change from baseline in the St. George's Respiratory Questionnaire (SGRQ) total score at Week 24 2. Proportion of SGRQ responders at Week 24	Regardless of whether the patient discontinues treatment prematurely and regardless of major protocol deviation, as per the Treatment Policy strategy.	1. Estimated treatment difference at the end of the double-blind period (and corresponding 95% CI) from ANCOVA analysis. 2. Odds ratio for proportion of responders with an improvement of at least 4 units at the end of the double-blind period (and corresponding 95% CI) from logistic

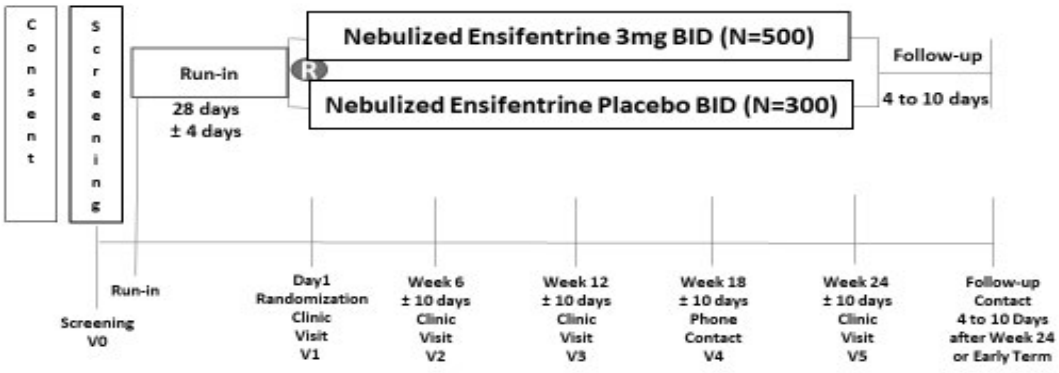
					regression analysis.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase III, multicenter, randomized, double-blind, parallel group, placebo-controlled study. A flow chart illustrating the key components of the study is provided in Figure 1:

Figure 1: Study Flow Chart



Approximately 800 patients with moderate to severe COPD aged 40 to 80 years (inclusive) will be stratified by two different factors: stable background maintenance long-acting muscarinic antagonist (LAMA) or long-acting beta-2 agonist (LABA) therapy use (yes or no) and cigarette smoking (current or former), then randomized 5:3 to receive ensifentrine (3 mg): placebo for 24 weeks. The background therapy strata will be capped at 50%. Up to 20% of patients are allowed to take inhaled corticosteroids during the study under certain provisions, as detailed in the sections 6.7.2 and 6.7.3 of the study protocol. Patients in the background maintenance LAMA or LABA therapy strata must withhold twice-daily maintenance LAMA or LABA (or LAMA/ICS or LABA/ICS) for 24 hours and once-daily maintenance LAMA or LABA (or LAMA/ICS or LABA/ICS) for 48 hours prior to initiation of any spirometry. All patients must withhold short-acting beta-2 agonist (SABA) rescue medication for at least 4 hours prior to initiation of any spirometry.

Patients are expected to take the study medication twice daily, administered via a standard jet nebulizer, during the study period. Schedule of in-clinic dosing can be found in section 1.4 of the study protocol.

3.2. SCHEDULE OF EVENTS

Schedule of activities can be found in section 1.3 of the study protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

Changes to analysis from protocol include:

- "COPD severity" added as a subgroup analysis.
- Per-protocol population definition updated to exclude patients that discontinued study medication before study day 74.
- Sections 9.4.1 and 9.4.4 in the protocol states, "A sensitivity analysis [on the proportion of responders on the SGRQ] will be performed in which patients with missing data at the required visit will be considered non-responder in the analysis", and "For the responder analysis of SGRQ, patients with no available data for imputation will be considered non-responders as a sensitivity analysis", respectively. However, a non-responder analysis may create an unintentional bias in favour of the treatment arm. I.e. if placebo patients discontinue, this technique may inadvertently set more values in the placebo arm to "non-responder". Therefore, this technique for missing data analysis will not be implemented.
- Analysis of E-RS total score responder, defined as a decrease from baseline in the week mean total of E-RS score of greater than or equal to 2, added in the Section 16.3.1.7.
- Analysis of Morning trough FEV_1 responder, defined as an improvement from baseline of 100 mL or more, added in the Section 16.3.1.8.
- Chronicity section removed from Adverse Events section.
- A sensitivity analysis will be performed for weekly mean E-RS total score, using ANCOVA approach, as described in section 16.2.4 of the SAP, in which all patients with baseline mean = 0 will be excluded.
- Due to the unreliability of the data, site [redacted] will be removed from efficacy and safety analyses in any section.
- Extended randomized, extended mITT and extended Safety populations set will be included as new populations to manage this site to be removed. Added in the Section 5.

4. PLANNED ANALYSES

A final analysis after DBL is planned for this study.

4.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC for this study.

4.2. INTERIM ANALYSIS

There is no interim analysis planned for this study, however additional patients may be randomized if:

- the SD has increased significantly from the estimated 250 mL, as per sponsor discretion, and/or
- the withdrawal rate at 24 weeks exceeds 25% overall, and the percentage of patients with missing FEV_1 over 12 hours at Week 12 in mITT (modified Intent-to-Treat) population exceeds 20% overall.

Note: As part of the primary endpoint analysis, SD of the treatment difference is calculated to check the sample size with 90% power.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following sponsor authorization of SAP (and associated output shells), DBL, analysis sets and unblinding of treatment.

The population PK analysis identified in the protocol will be performed separately by the assigned Verona Pharma Designee. A separate modeling data analysis plan will be prepared for the analyses and results will be reported separately from the clinical study report.

5. ANALYSIS SETS

Agreement and authorization of patients included/excluded from each analysis set will be conducted prior to the unblinding of the study. For PK set see sections 5.10 and 20 of the SAP. Analyses will be performed for the analysis sets described in Table 2.

Table 2: Analysis sets

	All Patients Enrolled Set	All Patients Random. Set	Extended Random. Set	Modified Intent-to-Treat Pop.	Extended modified Intent-to-Treat Pop.	Per-Protocol Pop.	Safety Set	Extended Safety Set	PK Set
Disposition of patients	X	X	X						

Protocol deviations		X							
Demographic and other baseline characteristics		X	X	X					
Surgical and medical history							X		
Prior and concomitant medication							X		
Compliance							X		
Efficacy: Primary endpoint				X	X	X			
Efficacy: Secondary endpoints				X	X	X			
Efficacy: Other endpoints				X	X				
Sensitivity Analyses				X	X	X			
Safety							X	X	
Pharmacokinetics									X

5.1. PROCESS FOR ANALYSIS SET ASSIGNMENT

Analysis set assignments and any associated reasons for analyses set exclusion will be described in the BDR plan and finalized within the BDR report prior to unblinding.

5.2. ALL PATIENTS ENROLLED SET

The all patients enrolled (ENR) set will contain all patients who provide informed consent for

this study. Patients will be classified according to randomized treatment with patients not randomized presented in a separate category, see APPENDIX 1.

5.3. ALL PATIENTS RANDOMIZED SET

The all patients randomized (RND) set will contain all patients in the ENR set who were randomized to study medication. For analyses and displays based on RND, patients will be classified according to randomized treatment. Site number [redacted] will be excluded from this population.

5.4. EXTENDED RANDOMIZED SET

The Extended randomized (RND) set will contain all patients in the ENR set who were randomized to study medication. For analyses and displays based on RND, patients will be classified according to randomized treatment. Site number [redacted] will be included in this population.

5.5. MODIFIED INTENT-TO-TREAT POPULATION

The mITT population will contain all patients in the RND set who received at least one dose (or partial dose) of study medication and patients will be classified according to randomized treatment. The intent-to-treat principle is preserved, despite the exclusion of patients randomized who did not take the study medication, because the decision of whether or not to begin the treatment could not be influenced by knowledge of the assigned treatment, i.e. the study medication is blinded. Site number [redacted] will be excluded from this population.

5.6. EXTENDED MODIFIED INTENT-TO-TREAT POPULATION

The Extended mITT population will contain all patients in the RND set who received at least one dose (or partial dose) of study medication and patients will be classified according to randomized treatment. The intent-to-treat principle is preserved, despite the exclusion of patients randomized who did not take the study medication, because the decision of whether or not to begin the treatment could not be influenced by knowledge of the assigned treatment, i.e. the study medication is blinded. Site number [redacted] will be included in this population.

5.7. PER-PROTOCOL POPULATION

The per-protocol (PP) population will contain all patients in the mITT who did not discontinue the study medication before study day 74, and did not experience any major/important PDs considered to have an impact on efficacy assessments involving lung function at week 12. Reasons for exclusion will be specified at a BDR meeting prior to DBL and may include violations of inclusion/exclusion criteria, violations of withdrawal criteria, incorrect randomization, use of prohibited medication, did not follow blinding procedures and non-compliance. Patients will be classified according to randomized treatment.

If protocol deviations in terms of dosing errors are detected post unblinding, these will lead to exclusion only if patient has received and used the opposite study drug compared to what was specified in the randomization and that this use occurred prior to week 12.

5.8. SAFETY ANALYSIS SET

The safety analysis (SAF) set will contain all patients in the RND set who receive at least one dose (or partial dose) of study medication and patients will be classified according to treatment received.
If there is any doubt whether a patient was treated or not, they will be assumed treated for the purposes of analysis. Site number [redacted] will be excluded from this population.

5.9. EXTENDED SAFETY ANALYSIS SET

The Extended safety analysis (SAF) set will contain all patients in the RND set who receive at least one dose (or partial dose) of study medication and patients will be classified according to treatment received.
If there is any doubt whether a patient was treated or not, they will be assumed treated for the purposes of analysis. Site number [redacted] will be included in this population.

5.10. PHARMACOKINETIC SET

The PK analysis set (PKAS) will include all patients randomized to ensifentrine, who receive at least one dose of ensifentrine, and have at least one quantified ensifentrine concentration at a scheduled PK time point after the start of dosing without important protocol violations and/or events with potential to affect PK concentrations.

The population PK analysis set will be defined separately in the modeling data analysis plan prepared by Verona Pharma/Designee.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE DATES AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.
Reference start date is defined as the day of the first dose of study medication (Day 1 is the day of the first dose of study medication) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference start date, then:
  Study Day = (date of event – reference start date) + 1.
- If the date of the event is prior to the reference start date, then:
  Study Day = (date of event – reference start date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix 2 of the SAP.

Reference end date is defined as the date of the last dose of study medication.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered baseline, unless time is present. If time of the assessment is on or after the study treatment start date, then the assessment is not considered baseline except in the following case: for main and responder SGRQ analysis, if the assessment on the day of randomization is done after dosing but prior to leaving the clinic after the 4 hour spirometry, the assessment is considered baseline. Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline, ECG abnormalities from pre-dose assessments and laboratory abnormalities from pre-dose draws that are analyzed externally post-dose are still considered baseline.

Baseline for the spirometry endpoints is defined as the mean of the 2 measurements taken pre-dose on Day 1 prior to reference start date and time, unless only 1 measurement is taken pre-dose on Day 1 prior to reference start date and time.

If the baseline visit is split across in 2 days with dosing on Day 1, then measurement from day – 1 will constitute baseline for spirometry endpoints.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented.

Patients who were a screen failure and received approval from the Medical Monitor for rescreening will go through all of the original screening assessments. Data from the latest rescreened visit will be used in the summaries, however all screening information will be listed. Rescreened patients will keep the same patient number, as for the initial screening. Unscheduled measurements will not be included in by-visit summaries but will contribute to the EOS value, or best/ worst case value where required (e.g. shift table).

Early termination data will be mapped to the next available visit number for by-visit summaries, as described in section 6.4 of the SAP.

Post-randomization if ECG result is Abnormal, Clinically Significant, then triplicate ECGs should be provided.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. WINDOWING CONVENTIONS

Each visit (except for Day 1 visit) will have a±10 days window. No visit windowing will be applied during the analysis to the data that is only collected at scheduled site visits for patients that have completed the study, and therefore the data will be presented as per the visit reported in the database.
For the patients that discontinued from the study, the End of Study (EOS) visit will be windowed to the corresponding visit, based on the study day, for questionnaire, spirometry and rescue medication data. The EOS visit can only be windowed to a visit that is missing or has a missing result. The rules for the windowing are described below.

- For spirometry raw data and derived data that happens at every visit, windowing will be done as per the corresponding visits.

- Day 1 = Day 1
- Week 6 = after Day 1 and up to and including Day 53
- Week 12 = after Day 53 and up to and including Day 95
- Week 24= after Day 95 and up to and including Day 179

- For spirometry derived data that only happen at certain visits, windowing will be done for the corresponding visits.
  - For morning trough:
    - Week 6 = after Day 1 and up to and including Day 53
    - Week 12 = after Day 53 and up to and including Day 95
    - Week 24= after Day 95 and up to and including Day 179
  - For evening trough and $AUC_{0\text{-}12h}$:
    - Week 12 = after Day 1 and up to and including Day 95
- For rescue medication data, E-RS/EXACT-PRO, e-diary data and COPD exacerbation, windowing will be done as per the corresponding visits.
  - For patients who completed the study or who discontinue study medication but continue in the study:
    - Week 1 = Actual study Day of Week 24 visit minus 168 days (inclusive) up to and including actual study day of week 24 visit minus 161 days
    - Week 2 = Actual study Day of Week 24 visit minus 161 days up to and including actual study day of week 24 visit minus 154 days
    - Week 3 = Actual study Day of Week 24 visit minus 154 days up to and including actual study day of week 24 visit minus 147 days
    - Week 4 = Actual study Day of Week 24 visit minus 147 days up to and including actual study day of week 24 visit minus 140 days
    - Week 5 = Actual study Day of Week 24 visit minus 140 days up to and including actual study day of week 24 visit minus 133 days
    - Week 6 = Actual study Day of Week 24 visit minus 133 days up to and including actual study day of week 24 visit minus 126 days
    - Week 7 = Actual study Day of Week 24 visit minus 126 days up to and including actual study day of week 24 visit minus 119 days
    - Week 8 = Actual study Day of Week 24 visit minus 119 days up to and including actual study day of week 24 visit minus 112 days
    - Week 9 = Actual study Day of Week 24 visit minus 112 days up to and including actual study day of week 24 visit minus 105 days
    - Week 10 = Actual study Day of Week 24 visit minus 105 days up to and including actual study day of week 24 visit minus 98 days
    - Week 11 = Actual study Day of Week 24 visit minus 98 days up to and

including actual study day of week 24 visit minus 91 days
- Week 12 = Actual study Day of Week 24 visit minus 91 days up to and including actual study day of week 24 visit minus 84 days
- Week 13 = Actual study Day of Week 24 visit minus 84 days up to and including actual study day of week 24 visit minus 77 days
- Week 14 = Actual study Day of Week 24 visit minus 77 days up to and including actual study day of week 24 visit minus 70 days
- Week 15 = Actual study Day of Week 24 visit minus 70 days up to and including actual study day of week 24 visit minus 63 days
- Week 16 = Actual study Day of Week 24 visit minus 63 days up to and including actual study day of week 24 visit minus 56 days
- Week 17 = Actual study Day of Week 24 visit minus 56 days up to and including actual study day of week 24 visit minus 49 days
- Week 18 = Actual study Day of Week 24 visit minus 49 days up to and including actual study day of week 24 visit minus 42 days
- Week 19 = Actual study Day of Week 24 visit minus 42 days up to and including actual study day of week 24 visit minus 35 days
- Week 20 = Actual study Day of Week 24 visit minus 35 days up to and including actual study day of week 24 visit minus 28 days
- Week 21 = Actual study Day of Week 24 visit minus 28 days up to and including actual study day of week 24 visit minus 21 days
- Week 22 = Actual study Day of Week 24 visit minus 21 days up to and including actual study day of week 24 visit minus 14 days
- Week 23 = Actual study Day of Week 24 visit minus 14 days up to and including actual study day of week 24 visit minus 7 days
- Week 24 = Actual study Day of Week 24 visit minus 7 days up to and including actual study day of week 24 visit

- For patients who discontinue the study before Week 24:
  - Week 1 = on or after Day 1 and up to and including Day 8
  - Week 2 = after Day 8 and up to and including Day 15
  - Week 3 = after Day 15 and up to and including Day 22
  - Week 4 = after Day 22 and up to and including Day 29
  - Week 5 = after Day 29 and up to and including Day 36
  - Week 6 = after Day 36 and up to and including Day 43
  - Week 7 = after Day 43 and up to and including Day 50
  - Week 8 = after Day 50 and up to and including Day 57
  - Week 9 = after Day 57 and up to and including Day 64
  - Week 10 = after Day 64 and up to and including Day 71

- Week 11 = after Day 71 and up to and including Day 78
- Week 12 = after Day 78 and up to and including Day 85
- Week 13 = after Day 85 and up to and including Day 92
- Week 14 = after Day 92 and up to and including Day 99
- Week 15 = after Day 99 and up to and including Day 106
- Week 16 = after Day 106 and up to and including Day 113
- Week 17 = after Day 113 and up to and including Day 120
- Week 18 = after Day 120 and up to and including Day 127
- Week 19 = after Day 127 and up to and including Day 134
- Week 20 = after Day 134 and up to and including Day 141
- Week 21 = after Day 141 and up to and including Day 148
- Week 22 = after Day 148 and up to and including Day 155
- Week 23 = after Day 155 and up to and including Day 162
- Week 24 = after Day 162 and up to and including Day 169

6.5. STATISTICAL TESTS

In general, unless stated otherwise, continuous variables will be summarized using descriptive statistics (number of patients, mean, standard deviation [SD], median, minimum and maximum values) and for categorical (nominal) variables, the number and percentage of patients will be used.

The default significant level will be 5%; CIs will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.6. COMMON CALCULATIONS

- Change from baseline: Test Value at Visit X – Baseline Value
- Percentage change from baseline:

$$\frac{\text{Test Value at Visit X} - \text{Baseline Value}}{\text{Baseline Value}} * 100\%$$

6.7. ACTUAL TREATMENT

Once the study unblinds, the patient's actual treatment will be assigned based on the most frequent medication they have received throughout the study. Patients are only expected to receive either 3 mg of ensifentrine, or placebo. The external vendor, Cenduit, will provide the Material List document after confirmation of a DBL. This document will contain the kit

numbers, which will be merged with the site data to obtain the treatment that was dispensed at each visit.
If a patient takes more than one medication and the ratio of actual treatments taking the placebo and ensifentrine is the same, then the patient will be assigned ensifentrine.

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

6.9. STRATA CALCULATIONS

There are two separate stratification factors used: background maintenance therapy strata and smoking strata. For both factors planned and actual will be created.
For background maintenance therapy strata:

- Planned – As recorded in the Cenduit report.
- Actual - As recorded in the "Concomitant medications" eCRF page: Patients that take LAMA or LABA (or LAMA/ICS or LABA/ICS) medication with start date being before or on randomization date and end date is either ongoing/post-randomization are classified as being on background maintenance therapy strata. Patients that do not meet this criteria will be classified as "No".

For smoking strata:

- Planned – As recorded in the Cenduit report.
- Actual – As recorded in the "COPD and Smoking History" eCRF page.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Fixed effects: treatment (ensifentrine, placebo), region (Europe, North America), visit (Day 1, Week 6, Week 12, Week 18, Week 24), visit*treatment, stable background maintenance of LABA or LAMA (or LAMA/ICS or LABA/ICS) therapy use (yes, no), cigarette smoking (current, former)

- Random effect: patient
- Covariate: baseline

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally. Randomization to treatment arms is not stratified by country/ center.

When specified, statistical analysis will be adjusted for geographic region. Geographic region will be categorized as shown in Table 3:.

Table 3: Geographic Regions

Geographic Region	Country
Europe	Belgium, Bulgaria, Denmark, Hungary, Poland, Slovakia, Estonia, Spain
North America	United States, Canada

7.3. MISSING DATA

Missing safety data will not be imputed.
All data collected during the scheduled visits for patients on-treatment and off-treatment, for patients with treatment withdrawal, as well as the end-of-study visits for patients withdrawing from the study will be used for analysis performed on the mITT and that the remaining missing values will be handled as described in sections 16.1.2, 16.2.2 and 16.3.2 of the SAP.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

To address multiplicity in the analysis of the endpoints, statistical testing of the primary endpoint and key secondary endpoints will be done in the hierarchical order (listed below). Initially the primary endpoint will be checked to see if comparison between active treatment and placebo is statistically significant. If yes, the first key secondary endpoint will be evaluated. If yes, the next key secondary endpoint will be evaluated. This process will continue until either all endpoints are evaluated, or if one of the endpoints' comparison is not significant. Order of the endpoints that will be used for the hierarchical testing:

1. Change from baseline FEV_1 to FEV_1 $AUC_{0\text{-}12h}$ at Week 12
2. Change from baseline FEV_1 to peak FEV_1 at Week 12
3. Change from baseline (i.e. mean over the last 7 days of run-in) to the mean weekly value at Week 24 in COPD symptoms, as measured by daily diary (E-RS™:COPD)
4. Change from baseline in the SGRQ total score at Week 24
5. Change from baseline FEV_1 to morning trough FEV_1 at Week 12
6. Change from baseline FEV_1 to average FEV_1 $AUC_{0\text{-}4h}$ at Week 12
7. Proportion of SGRQ responders at Week 24

7.5. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in the efficacy analysis and disposition sections. Primary aim for the subgroup analysis is to check whether there are differences in treatment effect between strata or subgroups, which will be tested through interaction. For each analysis

by subgroup the results will be summarized as follows:

- Complete data with added fixed effect to the model: subgroup*treatment.
- Data split by subgroup using the main model.

The following subgroups will be assessed and described within the analysis sections 16.1.4 and 16.2.4 of the SAP.

- Gender at birth:
  - Female
  - Male
- Age-class (years):
  - <65
  - ≥65
- Region
  - Europe
  - North America
- Actual Background medication strata
  - Yes
  - No
- Actual Smoking strata
  - Current
  - Former
- Actual ICS use
  - Yes
  - No
- Known chronic bronchitis
  - Yes
  - No
- FEV_1 reversibility at screening (≥12% and ≥200mL increase in FEV_1)
  - Yes
  - No
- COPD severity
  - Moderate (50% ≤ post-bronchodilator FEV_1 at screening < 80% predicted)
  - Severe (30% ≤ post-bronchodilator FEV_1 at screening <50% predicted)
  - Very severe (post-bronchodilator FEV_1 at screening <30% predicted)

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.
The shells document provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study.
Cenduit will be the primary source for the randomization information.

9.1. DISPOSITION

Patient disposition and withdrawals will be presented for the RND set. Study medication and study withdrawals of patients will be presented by the date of the "End of Treatment/Disposition" page of the eCRF date of study withdrawal will be last available date within eCRF, the date of study medication withdrawal will be identified from End of Treatment page of the eCRF.

The number of study withdrawals and study medication withdrawals over the study will be summarized by treatment group and analyzed and presented through Kaplan-Meier plot using log-rank test, as described in section 16.3.3 of the SAP.
Time to study medication discontinuation by subgroups of actual background medication strata and actual smoking strata will be presented through Kaplan-Meier plot.

Reasons for exclusion from each analysis set, as well as patients not meeting eligibility and randomization criteria will be presented for the ENR set with patients classified according to the randomized treatment. Patients not randomized will be presented in a separate category.

9.1.1. DERIVATIONS

Study day of early study medication discontinuation = Last day of study medication intake - First day of study medication intake + 1.

Study day of early study discontinuation = Last day in the study - First day of study medication intake + 1.

Visit for discontinuation will be presented using four subgroups (Not treated, ≥ day 1 and ≤

week 6, > week 6 and ≤ week 12 and > week 12 and ≤ week 24), using the corresponding visit day windowing:

- week 6 = study day 53
- week 12 = study day 95
- week 24 = study day 179

9.2. PROTOCOL DEVIATIONS

PDs will be defined in the BDR report and the list will be finalized before the DBL.

9.3. EVALUATION INCLUDING EXCLUDED SITES

Site [redacted] was removed from the Randomized set. As a check of this exclusion, the patient disposition will be performed in the Extended Randomized set.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the RND. If there is a difference in patients between RND and mITT population, then demographic data and other baseline characteristics will also be presented for mITT.
Demographic data and other baseline characteristics will also be presented by subgroups of actual background medication strata and actual smoking strata for mITT.
No statistical testing is planned be carried out for demographic or other baseline characteristics.
The following demographic and other baseline characteristics will be reported for this study:

- Age (years)
- Age-class (years) (<65, ≥65)
- Gender at birth
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino (subgroup for rest of categories), Not Reported)
- Race
- Country
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- FEV_1 reversibility at screening (yes, no)
- Modified Medical Research Council (mMRC) questionnaire score

- Pre- and post-bronchodilator FEV_1 (both in liters and in percentage of predicted normal)
- Post-bronchodilator FEV_1/forced vital capacity (FVC)
- Time since initial diagnosis of COPD (years)
- Background medication strata [yes (subgroup for yes: LAMA, LAMA/ICS, LABA, LABA/ICS), no] –actual
- Known to have Chronic Bronchitis (yes, no)
- Known to have Emphysema (yes, no)
- Smoking strata (current (also includes stopped less than 6 months), former – stopped greater than 6 months ago) –actual recorded in the eCRF
- Number of cigarettes per day, Number of years smoking, Number of Pack Years
- COPD severity based on post-bronchodilator FEV_1 (Moderate, Severe, Very severe)

10.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$
- Time since initial diagnosis of COPD = (date of consent – date first diagnosed)/365.25
- Pack Years = Number of packs per day x number of years smoking

Reversibility status is calculated based on pre-bronchodilator and post-bronchodilator FEV_1 values taken at Screening. If patient has increase of ≥12% and ≥200mL then patient is reversible, else patient is non-reversible.

Age (years) collected in the eCRF will be used for the analysis.

Pack Years is automatically calculated in the eCRF and this value will be used in the summaries.
COPD severity will be derived as follows based on post-bronchodilator screening spirometry:

- Mild: post-bronchodilator $FEV_1 \geq 80\%$ predicted
- Moderate: $50\% \leq$ post-bronchodilator $FEV_1 < 80\%$ predicted
- Severe: $30\% \leq$ post-bronchodilator $FEV_1 < 50\%$ predicted
- Very severe: post-bronchodilator $FEV_1 < 30\%$ predicted

10.2. EVALUATION INCLUDING EXCLUDED SITES

As a check of the exclusion of site [redacted] from mITT, the demography and baseline disease characteristics will be performed in the mITT Extended.

- [redacted]

11. SURGICAL AND MEDICAL HISTORY

Surgical and Medical History information will be presented for the SAF set.

- Surgical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary. The version of MedDRA to be used will be specified prior to database lock. Data captured on the "Surgical Procedure History" page of the eCRF will be presented by System Organ Class (SOC) and Preferred Term (PT) for each treatment group.
- Medical History will be coded using MedDRA central coding dictionary. The version of MedDRA to be used will be specified prior to database lock.
    - Medical History conditions, captured on the "Medical History" page of the eCRF, are defined as those conditions which stop prior to or at Screening visit and will be presented by SOC and PT for each treatment group.

12. CONCOMITANT ILLNESSES

Concomitant illnesses will be presented for the SAF set.

- Concomitant Illnesses will be coded using MedDRA central coding dictionary. The version of MedDRA to be used will be specified prior to database lock.
    - Concomitant Illnesses, captured on the "Medical History" page of the eCRF, are conditions which started prior to the first treatment dose and are ongoing at the date of first treatment dose, and will be presented by SOC and PT for each treatment group.
    -

13. MEDICATIONS

Prior, prior concomitant and concomitant medications will be presented separately for the SAF set and coded using the World Health Organization (WHO) drug code and summarized by Anatomical Therapeutic Clinical Classification System (ATC) levels 1, levels 2 and 4. Possible therapeutic subgroups include ICS, LABA, LAMA, corticosteroids, short-acting B2 agonist, short-acting anti-muscarinic and combinations specified below, which are defined in a separate spreadsheet provided by the medical data reviewer. Combinations to be analyzed:

1. Oral or intravenous (IV) Corticosteroids
2. Oral or IV Corticosteroid & Other combinations
3. LAMA
4. LAMA/LABA

5. LAMA & OTHER COMBINATIONS
6. LABA
7. LABA & Other combinations
8. ICS/LAMA/LABA or ICS/LABA/LAMA
9. ICS/LAMA
10. ICS/LABA
11. ICS & Other Combinations
12. SABA/Short-Acting Anti-Muscarinic
13. SABA
14. SABA & other combinations
15. SABA/ICS
16. SABA/ Corticosteroid
17. Short-Acting Anti-Muscarinic

See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

- 'Prior' medications are medications which started prior to the first dose of study medication and stopped prior to the first dose of study medication.
- 'Prior Concomitant' medications are medications which started prior to the first dose of study medication and ended on or after the date of first dose of study medication or were ongoing at the end of the study.
- 'Concomitant' medications are medications which:
    - started on or after the first dose of study medication and started no later than last day of study medication intake,
    - AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.
- 'Post' medications are medications which started from the day after the last dose of study medication.

Prior, prior concomitant and concomitant COPD medications will be presented separately for the SAF set. COPD medications are those provided by medical review and will be presented as preferred term and ATC levels 1, levels 2 and 4.

Data captured on the "Concomitant Medications" page of the eCRF will be presented for each treatment group. Patients with multiple medications within an ATC/ therapeutic subgroup will only be counted once for that level.

Oxygen therapy and CPAP will be listed separately to other medications. Oxygen therapy is defined by ATC code: "V03AN" and route is not Oral; CPAP is defined by ATC code: "R07AX" and route is not Oral.

14. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be presented for the SAF set.

The dates of first dose of study medication administration will be taken from the "Drug Exposure" page of the eCRF (Day 1). The date of last dose of study medication administration will be taken as the latest date among all from the "Drug Exposure" and "Drug Exposure – Evening Blinded Study Medication Clinic Dosing" pages of the eCRF.
If no drug exposure were made at last visit and the dispensed drug supply was insufficient to cover use up to last visit, the last exposure day will be set to the day the drug supply should have been empty if patient had been compliant to twice daily regimen.
Interruptions and compliance are not taken into account for duration of exposure.

Study medication exposure will be presented using summary statistics by total number of days, and using frequency counts by subgroups: 1-42 days, 43-84 days, 85-126 days, 127-168 days and >168 days.

14.1. DERIVATIONS

Duration of exposure (days) = date of last study medication administration – date of first study medication administration + 1.

15. COMPLIANCE

Compliance to study medication based on dispensed and returned unused ampules and secondarily based on e-Diary entries will be presented for the SAF set.

Compliance will be presented using summary statistics by time intervals (Day 1 to Week12, Weeks 12-24 and full study length), as well as using frequency counts by subgroups: <50%, 50-70%, 70-80%, 80-90%, 90-100% and >100%.

15.1. STUDY MEDICATION COMPLIANCE

Study medication compliance will be summarized by treatment group in 2 ways:

- The number of ampules dispensed and unused returned will be taken from "Drug Accountability" page of the eCRF.
- Drug intake as recorded in the e-diary.

Patient is non-compliant, for study medication intake collected through the number of ampules dispensed/returned, if identified as taking less than or equal to 70% of blinded study medication during the period Day 1 to Week 12, or less than or equal to 50% over the study (Day 1 to Week 24). Calculations will not include time after treatment withdrawal.

15.1.1. DERIVATIONS

Compliance with study medication will be calculated on the number of ampules count (total dispensed – total returned) divided by the prescribed number of ampules expressed as a percentage, see calculations below.

Patient should take the study medication twice daily and record it in their e-Diary apart from Week 24 visit when patient's last dose will be in the morning.

Patients are dispensed ampules at Visit X and return at Visit X+1, however in the eCRF returned ampules will be recorded under Visit X.

- For time interval compliance to study medication will be calculated as follows:

$$\frac{([\text{N of Ampules dispensed at Visit X}] - [\text{N of Ampules returned at Visit Y}])}{\text{Denominator1}} * 100$$

Where Denominator1 is calculated with the following rules:

  - N_1 = Number of ampules expected calculated based on total N of Ampules dispensed, taking into account 2 ampules per day, apart from last dose date for completed patients where we would only consider 1 ampule per day.
  - For non-Week 24 return ampules visit: N_2 = Number of ampules between dispensing and returning visit calculated: {[Date of Visit Y] - [Date of Dispensing at Visit X]+1}* 2.
  - For Week 24 return ampules visit: N_2 = Number of ampules between dispensing and returning visit calculated: {{[Date of Visit Y] - [Date of Dispensing at Visit X]+1}* 2}-1.

- If $N_1 \geq N_2$ then Denominator1 = N_2.
- If $N_1 < N_2$ then Denominator1 = N_1.

- Overall Compliance to study medication will be calculated as follows:

$$\frac{(\text{N of Ampules total dispensed} - \text{N of Ampules total returned})}{\text{Denominator2}} * 100$$

Where Denominator2 is calculated with the following rules:

- N_1 = Number of days calculated based on total N of Ampules dispensed, taking into account 2 ampules per day, apart from last dose date for completed patients where we would only consider 1 ampule per day.
- N_2 = Number of days between dispensing and returning visit calculated: {{[Date of Visit X(n)] - [Date of Dispensing at Visit 1]+1}* 2}-1.
- If $N_1 \geq N_2$ then Denominator2 = N_2.
- If $N_1 < N_2$ then Denominator2 = N_1.

For patients who permanently discontinue the study medication, the "Date of Visit X(n)"/ "Date of Visit Y" will be replaced by the last dose date of study medication, as specified in section 14 of the SAP. Whereas for patients who completed study, the "Date of Visit X(n)"/ "Date of Visit Y" will be replaced by date of last dose.

Drug intake as recorded in the e-diary: percent of 'yes' responses. The denominator is the number of records for which the patient provided an answer (Yes or No) to drug intake questions (morning and evening) in the e-diary.
For time interval study medication e-diary compliance, use week's windowing conventions described in section 6.4 of the SAP. Use study day assigned to determine the date for weeks required or the time intervals, Week 12 and Week 24. The compliance will be calculated as follows:

$$\frac{(\text{Week X}^* < \text{number of 'yes' responses entered in the eDiary} \leq \text{Week Y})}{(\text{Week X}^* < \text{number of non} - \text{missing responses entered in the e} - \text{Diary} \leq \text{Week Y})} * 100$$

*If Week X = Day 1, update "<" to be "≤". If Week Y is Week 24 and patient has completed treatment then the last entry we expect in the morning. Patient should not log any entries from and including evening of Week 24.

15.2. E-DIARY COMPLIANCE

The flow of the eDiary entries patient has to follow is:

1. E-RS
2. Study medication compliance
3. Background medication compliance (if applicable)
4. Rescue medication use

Based on this, we can assess if patient has been compliant with their E-RS questions, based on their study medication compliance and therefore no further E-RS compliance needs to be assessed.

15.2.1. DERIVATIONS

E-diary compliance will be calculated as per the following. Use study day assigned to determine the date for each week, as pe the windowing conventions described in section 6.4 of the SAP:

$$\frac{(\text{Week X}^{*} < \text{number of days study medication data was entered in the e} - \text{Diary} \leq \text{Week Y})}{[\text{Study Day at Week Y}] - [\text{Study Day at Week X}\} + 1} * 100$$

*If Week X = Day 1, update "<" to be "≤".

16. EFFICACY OUTCOMES

16.1. PRIMARY EFFICACY

The primary efficacy analysis will be performed for the mITT population.

16.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy variable is change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12.
FEV_1 data captured in the eResearch Technology (ERT) database will be used for the model in determining baseline value and for AUC calculation.

16.1.1.1. $AUC_{0\text{-}T}$

Spirometry (FEV_1) will be performed at Screening and the following time points during, each treatment:

[redacted]

- Day 1: ≤40 minutes pre-dose (2 measurements); 30 minutes, 1, 2 and 4 hours post-dose.
- Week 6 and Week 24: ≤40 minutes pre-dose; 30 minutes, 1, 2 and 4 hours post-dose.
- Week 12 and Early Termination: ≤40 minutes pre-dose; 30 minutes, 1, 2, 4, 6, 8 and 12 hours post-dose.

Baseline FEV_1 is the mean of the two measurements taken before study medication on the day of first dosing, i.e. ≤40 minutes pre-dose on Day 1.

The average effect will be calculated as the AUC divided by the length of the time interval of interest (for example, 12 hours for $AUC_{0\text{-}12h}$ or 4 hours for $AUC_{0\text{-}4h}$). AUC will be calculated using the trapezoidal method, as follows:

$$\mathrm{AUC} = \frac{1}{2}\sum_{i=1}^{n-1}(T_{i+1} - T_i)(C_{i+1} + C_i)$$

Where Ti is the ith time value, Ci is the ith effect value, n is the number of time values. The change from the baseline FEV_1 to average FEV_1 (AUC) will be summarized and analyzed.
If two last data points are missing the AUC is set to missing, that is for $AUC_{0\text{-}12h}$ we require at least up to 8 hours of assessments and for $AUC_{0\text{-}4h}$ we require at least up to 2 hours of assessments. This would mean if we only have 8 hours of assessments, then we would calculate $AUC_{0\text{-}8h}$, however it would still be labelled as $AUC_{0\text{-}12h}$. If there is no pre-dose measurement available for the calculation of the AUC, then the AUC will not be calculated. The pre-dose measurement used in the calculation of AUC is the latest value measured ≤40 minutes pre-dose. The pre-dose value will be used as time 0 when computing $AUC_{0\text{-}T}$.
For $AUC_{6\text{-}12h}$ we require at least the 6-hour and 12-hour timepoint for analysis.

16.1.2. Missing Data Methods for Primary Efficacy Variable

The main analysis for the primary endpoint will include estimates from missing data imputation described below. This is done to investigate the influence of missing data due to drop-outs. Only patients with non-missing baseline will be included in the analysis.
The primary analysis will be analyzed using MI based on the missing data assumption Missing at Random (MAR). This process will follow four steps:

1. Partially impute the data for a monotone missing pattern with 100 as a number of imputations and "20905" as seed number. Employ the Markov Chain Monte Carlo (MCMC) method with treatment, region, background medication strata, smoking strata, baseline FEV_1 and average FEV_1 $AUC_{0\text{-}12h}$ at Week 12.
   The following SAS codes will be used:

```
proc mi data=<data1> out=<data2> nimpute=100 seed=20905;
```

```
    var <treatment>  <region>  <BackgroundMedStrata>  <SmokingStrata>
    <baseline>  <visits>;
    mcmc impute=monotone chain=multiple;
run;
```

2. Impute the monotone data using a regression imputation model. Apply by imputation using seed number "20905" with treatment, region, background medication strata, smoking strata, baseline FEV_1 and average FEV_1 $AUC_{0\text{-}12h}$ at Week 12.
   The following SAS codes will be used:

```
proc mi data=<data2> out=<dataout> nimpute=1 seed=20905;
      by _imputation_;
      class <treatment>  <region>  <BackgroundMedStrata>
      <SmokingStrata>;
      var <treatment>  <region>  <BackgroundMedStrata>
         <SmokingStrata> <baseline>  <visits>;
      monotone regression;
run;
```

3. Each multiple imputed dataset in Step 2 will be analyzed separately, as described in section 16.1.3 of the SAP.
4. The estimates (LS means, SE, CI, and p-value) from the model analysis in Step 3 will be combined using Rubin's combination rules for statistical inference.

Sensitivity analysis will be done using:

- Average imputation will be based on data collected on treatment at required visit, or at early termination visit. This will be done on patient level. If there is no such data available, impute with average change from baseline for the particular visit in the opposite randomized treatment group.
- Tipping point approach will repeat the ANCOVA analysis, under Missing not at Random (MNAR) assumption, to assess the robustness of p-value significance. In case the original analysis will produce a p-value<0.05, then the imputed values will be adjusted by a value k (positive) added or subtracted (depending on what worsens the endpoint) to the endpoint of the patients in Ensifentrine group (worsening results) and added or subtracted (depending on what improves the endpoint) from the endpoint of the patients in placebo group (improving results). The value for k is determined by adjusting the bias starting with a value of 0.01 and increasing it with increments of 0.01 until p-value obtained from MI method is no longer statistically significant (p-value>0.05). Seed number used will be the same as for MI analysis, "20905". If the primary analysis is not significant (p-value>0.05), then the tipping point is reversed by determining value for k by adjusting the bias until p-value≤0.05. If the p-value<0.05 with more improvement in the placebo group comparably

to Ensifentrine group, then the tipping point is reversed by adjusting until there will be no more treatment difference between groups.

16.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary objective of this study is to test the hypothesis that there is a difference between ensifentrine in comparison with placebo.

The change from baseline FEV_1 to average FEV_1 $AUC_{0\text{-}12h}$ will be compared between ensifentrine and placebo using ANCOVA with fixed effects for treatment, region, background medication strata and smoking strata and baseline FEV_1 as covariate. Missing data will be imputed using imputation described in section 16.1.2 of the SAP. The estimated treatment difference will be presented with 95% CI and associated p-value. Furthermore, SD will be presented for the treatment difference to check the sample size with 90% power.
Summary statistics will be performed on the imputed values.

Model assumptions will be tested as per the following rules on the blinded data, before the DBL.

1. Residual vs Predicted plots will be created to check residuals are uncorrelated and normally distributed.
2. Normality of the data will be checked using Kolmogorov-Smirnov normality test.

If any of the checks specified above fail the test, then alternative approaches will be discussed, including different ways of transposing data. The SAP will be updated to reflect any changes prior to DBL.

Only spirometry measurements with best test review (BTR) grades “Acceptable” and “Borderline Acceptable” are used in the analysis and baseline calculations.

16.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary endpoint will be presented for the following:

- Subgroup analysis will be performed by subgroups, including data imputation described in sections 7.5 and 16.1.2 of the SAP, respectively.
- Observed data analysis will be performed by the following subgroups:
  - Analysis with no data imputation, including all patients with data collected, on treatment or not, and at required timepoint or at EOS visit (excluding patients with missing data).
  - Analysis with no data imputation, including only patients with data collected at the

required visit while still on randomized treatment at scheduled visit, or at end of study visit within the visit window.

- Average imputation, as described in section 16.1.2 of the SAP.
- Analysis with tipping point approach, as described in section 16.1.2 of the SAP.
- Analysis with multiple imputation, as described in sections 16.1.2 and 16.1.3 of the SAP, based on PP population.

16.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed for the mITT population.
These include:

- Change from baseline FEV_1 to peak FEV_1 on Day 1 and at Weeks 6, 12 and 24
- Change from baseline (i.e. mean over the last 7 days of run-in) to the mean weekly value at Weeks 6, 12 and 24 in COPD symptoms, as measured by daily diary (E-RS^{TM}:COPD)
- Change from baseline in the SGRQ total score at Weeks 6, 12 and 24
- Change from baseline FEV_1 to morning trough FEV_1 at Weeks 6, 12 and 24
- Change from baseline FEV_1 to average FEV_1 AUC_{0-4h} on Day 1 and at Weeks 6, 12 and 24
- Proportion of SGRQ responders at Weeks 6, 12 and 24
- Change from baseline (i.e. mean over the last 7 days of run-in) to the mean weekly value in the number of puffs of rescue medication at Weeks 6, 12 and 24
- TDI questionnaire at Weeks 6, 12 and 24
- Change from baseline FEV_1 to evening trough FEV_1 at Week 12

16.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

16.2.1.1. Spirometry

Spirometry measurement's best test time which is used in the analysis is measured in ERT and first time for spirometry measurements is measured in the eCRF and will be listed alongside the ERT best time.

Peak FEV_1 will be computed as the maximum value in the 4 hours after dosing (4 timepoints after dosing: 30 minutes, 1 hour, 2 hours and 4 hours). Baseline FEV_1 is the average of the two measurements taken before study medication on the day of first dosing, i.e. ≤40 minutes pre-dose on Day 1.

Average FEV_1 AUC_{0-4h} is calculated as described in section 16.1.1.1 of the SAP.

Morning trough FEV_1 is the last value collected prior to the morning dose.
Evening trough FEV_1 is the value collected at the 12 hours post-morning dose timepoint and prior to the evening dose.

All measurements, including unscheduled measurements, within specified time period will be used for deriving parameters; for scheduled 12 hours post-morning dose measurement use regardless of being within specified time period.

16.2.1.2. Questionnaires

16.2.1.2.1. E-RS^{TM}:COPD

EXACT-Respiratory Symptoms for COPD (E-RS^{TM}: COPD) data will be collected within EXACT-PRO questionnaire (consisting of 14 questions), as shown in Appendix 3. Please note that items 3, 8, 9, 10, 11 and 14 have separate scoring instructions, namely with the same raw score being assigned to several answer options. E-RS^{TM}: COPD consists of 11 questions, with subdomains of: Breathlessness, Cough and Sputum, and Chest Symptoms. This data will be collected everyday throughout the duration of the study.

Calculating the score
E-RS subdomains:

- Breathlessness – items 7, 8, 9, 10 and 11 (score range: 0-17)
- Cough and Sputum – items 2, 3 and 4 (score range: 0-11)
- Chest Symptoms – items 1, 5 and 6 (score range: 0-12)

The E-RS Total score is derived as the sum of the raw scores of the 11 items (score range: 0-40). Total and subdomain scores are derived weekly as the mean over the days within each window, as specified in the section 6.4 of the SAP, using only days where data was recorded. Baseline is the mean over the 7 days prior to the first intake of study treatment, using only days where data was recorded. If less than 4 days of data are available for the week, the weekly mean is set to missing. Furthermore, all questions need to be answered to be evaluable for that day.
If a patient discontinued then use treatment study end date, as the date of their last expected visit.

The EXACT-PRO total score will be calculated by first summing the raw scores of all 14 items (score range: 0-51) and then looking up the corresponding EXACT-PRO total score in the table described in the APPENDIX 4 (converted score range: 0-100).

E-RS subdomain score is calculated as the sum from the relevant questions.

16.2.1.2.2. SGRQ

St. George's Respiratory Questionnaire (SGRQ) is a questionnaire consisting of 17 questions, split into two parts. Part 1 consists of the first 8 questions and is related to the Symptoms subdomain. The remaining 9 questions are in Part 2, which are related to the Activity and Impacts subdomains. Each possible answer to each question has a weight assigned described in the APPENDIX 5.

Note that question 6 (How long did the worst respiratory attack last?) has an additional instruction, "Go to Question 7 if you did not have a severe attack". If question 6 has not been answered, it will be assigned a weight of zero.

Calculating the score
Subdomains:

- Symptoms – items 1 to 8
- Activity – items 11 and 15
- Impacts – items 9, 10, 12, 13, 14, 16 and 17

The score for each component is calculated separately by dividing the summed weights by the maximum possible weight for that component and expressing the result as a percentage. It is not possible to have missing items in the questionnaire, as the data are collected in an electronic tablet which doesn't allow patients to skip between items.

$$Component\ score = 100 * \frac{Sum\ of\ weights\ from\ all\ positive\ items\ in\ that\ component}{Sum\ of\ maximum\ weights\ for\ all\ items\ in\ that\ component}$$

The total score is calculated similarly

$$Total\ score = 100 * \frac{Sum\ of\ weights\ from\ all\ positive\ items\ in\ that\ questionnaire}{Sum\ of\ maximum\ weights\ for\ all\ items\ in\ that\ questionnaire}$$

The higher the score the more severe impact of COPD on patient's life.

Sum of maximum possible weights for each component and Total:
Symptoms = 662.5
Activity = 1209.1
Impacts = 2117.8
Total = 3989.4

16.2.1.2.3. BDI/ TDI

Baseline Dyspnea Index (BDI) and Translational Dyspnea (TDI) are questionnaires that focus on three subdomains: Functional impairment, Magnitude of task and Magnitude of effort. BDI is collected at baseline (Day 1) and TDI is collected post-baseline (Weeks 6, 12 and 24).

Subdomain score is calculated as the sum from the related questions.
Total score is calculated as the sum of the subdomain scores.

If at least one of the scores is missing, then total score is set to missing.

16.2.1.3. Rescue Medications

Baseline use of rescue medication is the mean over the last 7 days of run-in phase, using only days where data was recorded:

$$\frac{Sum\ of\ number\ of\ puffs\ taken}{days\ recorded}$$

Use of medication per week is calculated as the mean use daily over 7 days, as described in the windowing conventions section of the SAP, calculated only based on the days data was recorded/verified.
If less than 4 days of data are available for the week, the weekly mean is set to missing.
If a patient discontinued then use study discontinuation end date, as the date of their last expected data input.
This will be documented as Albuterol/Salbutamol in the "Rescue Medication" page of the eCRF, as well as in the "Rescue Medication Use" diary entry.
The rescue medication use will be confirmed in the diary using the following rules:

1. If patient has put in rescue medication use then analyze as expected
2. If patient has not put in rescue medication use, then to confirm that there was no diary compliance issue, or IT issue, question "No Rescue Medication Confirmation" will be checked to make sure it is filled in correctly.
3. If patient has not put in rescue medication use and question "No Rescue Medication Confirmation" was not filled in correctly then this will be treated as diary compliance or IT issue and therefore this day will not be used as the day recorded for the weekly means calculation.

16.2.2. Missing Data Methods for Secondary Efficacy Variables

16.2.2.1. MI method – continuous data

The analysis for key secondary endpoints (FEV_1 $AUC_{0\text{-}4h}$, peak FEV_1, morning trough FEV_1, SGRQ total score and weekly mean E-RS total score) and for evening trough FEV1 and weekly rescue medication will be performed using MI based on the missing data assumption MAR.
This process will follow four steps (below the example uses baseline FEV_1, but it is repeated also for baseline of other key secondary endpoints mentioned above, excluding the ones evaluated weekly):

1. Partially impute the data for a monotone missing pattern with 100 as a number of

imputations and "20905" as seed number. Employ the Markov Chain Monte Carlo (MCMC) method with treatment, region, background medication strata, smoking strata, baseline FEV_1 and <Visit data>. <Visit data> corresponds to all scheduled visits available for the parameter analyzed. Each visit will correspond to a covariate within the model.
The following SAS codes will be used:

```
proc mi data=<data1> out=<data2> nimpute=100 seed=20905;
    var <treatment>  <region>  <BackgroundMedStrata>  <SmokingStrata>
    <baseline>  <visits>;
    mcmc impute=monotone chain=multiple;
run;
```

2. Impute the monotone data using a regression imputation model. Apply by imputation using seed number "20905" with treatment, region, background medication strata, smoking strata, baseline FEV_1 and <Visit data>.
The following SAS codes will be used:

```
proc mi data=<data2> out=<dataout> nimpute=1 seed=20905;
      by _imputation_;
      class <treatment>  <region>  <BackgroundMedStrata>
      <SmokingStrata>;
      var <treatment>  <region>  <BackgroundMedStrata>
         <SmokingStrata> <baseline>  <visits>;
      monotone regression;
run;
```

3. Each multiple imputed dataset in Step 2 will be analyzed separately, as described in section 16.2.3 of the SAP.
4. The estimates (LS means, SE, CI and p-value) from the model analysis in Step 3 will be combined using Rubin's combination rules for statistical inference.

Note: For secondary endpoints that are evaluated weekly, the following updates will be implemented for the first 2 steps:

1. MI model will contain weekly means at all weeks available to impute the data to create a monotone missingness pattern, so will be imputed missing values at any week (i.e Week 1, Week 2, etc.).
2. After this, the fully imputed dataset will include weekly means at weeks corresponding to scheduled visits in the MI model, and also only impute missing values at weeks corresponding to scheduled visits.

16.2.2.2. MI method – binary data

For the analyses of proportion of SGRQ, weekly mean total E-RS and Morning trough FEV_1 responders, an analysis will be performed using MI based on the missing data assumption MAR. This process will impute the continuous underlying data, as per 16.2.2.1 (morning trough FEV_1, SGRQ total score and weekly mean total E-RS), and then recalculate the binary outcome of responder or non-responder. The analysis will follow the steps below (Ratitch and O'Kelly, 2014, pp.124 - 127) (below the example uses morning trough FEV_1, but it is repeated also for other endpoints mentioned above):

1) Follow steps 1 and 2 from 16.2.2.1 for the continuous morning trough FEV_1 results.
2) For the imputed results re-calculate response, where a response is an improvement from baseline in morning trough FEV_1 of 100 mL.
3) Analyse each multiply imputed dataset separately, as described in section 16.2.3 of the SAP, producing LS Means, odd ratios and corresponding 95% confidence interval and p-value.
4) For the odds ratios:
   a) Before applying Rubin's rule, apply a normalising transformation to the odds ratios as well as their standard errors. The distribution of the log of odds ratios approximates to a normal distribution. Therefore, calculate the transformed values, where OR is odds ratio, Lower/Upper CL are the confidence interval estimates of the ORs:

$$OR_{norm} = \log(OR)$$

$$SE_{norm} = \frac{(\log(Upper\ CL) - \log(Lower\ CL))}{(2 \times 1.96)}$$

   b) Appy Rubin's rule with PROC MIANALYZE to the transformed odds ratios with corresponding transformed standard errors.
   c) Back-transform the combined results as follows:

$$OR_{bt} = exp^{OR_{norm}}$$
$$Lower\ CL_{bt} = OR_{bt} \times e^{(-1.96 \times SE_{norm})}$$
$$Upper\ CL_{bt} = OR_{bt} \times e^{(1.96 \times SE_{norm})}$$

5) For the odds of response per treatment arm
   a) Take the LS means to be estimates of the log-odds of response per treatment arm and assume that they asymptotically tend to a normal distributions.

b) Appy Rubin's rule with PROC MIANALYZE to the LS means.
c) Transform the combined results by exponentiating to get the odds of response per treatment arm.

16.2.2.3. MI method – range data

The sensitivity analysis for key secondary endpoints (SGRQ total score and weekly mean E-RS total score), the main analysis of TDI and EQ-5D-5L will be performed using MI based on the missing data assumption MAR as described in the section 16.2.2.1 of the SAP. Additionally, in the first 2 steps the MIN= and MAX= options will be used to restrict the possible values that can be drawn referred to each endpoint (Laura Rodwell, 2014).

16.2.2.4. Other methods

As a sensitivity analysis, other missing data method for key secondary endpoints will follow the average imputation and tipping point approach taken for primary endpoint outlined in section 16.1.2 of the SAP.

16.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

16.2.3.1. Change from baseline variables, incl. TDI

All variables used in change from baseline analysis (incl. average FEV_1 $AUC_{0\text{-}4h}$, peak FEV_1, morning trough FEV_1, evening trough FEV_1, mean weekly E-RS™: COPD, SGRQ, mean weekly rescue medication and TDI) will be analyzed using ANCOVA approach, as described in section 16.1.3 of the SAP. BDI will be used as a baseline for TDI. Missing data will be imputed using imputation described in section 16.2.2.3 of the SAP.
Model assumptions will be tested and solved, if failed, as per section 16.1.3 of the SAP.

A plot of the mean change from baseline FEV1 to each post-dose FEV1 result over time will be created by subgroups of actual background medication strata and actual smoking strata, visit and treatment group.
A plot of the least squares means change from baseline to event over time will be presented (based on the ANCOVA analysis). Events will include weekly mean total E-RS score, SGRQ and weekly mean rescue medication use.

Only FEV_1 measurements with BTR grades "Acceptable" and "Borderline Acceptable" are used in the analysis.

16.2.3.2. Proportion of SGRQ total responders

Proportion of responders, with an improvement from baseline in SGRQ total score of 4 or more will be analyzed using a logistic regression model with fixed effects for treatment, region, actual background medication strata and actual smoking strata at baseline and baseline SGRQ total score as covariate. Missing data will be imputed as described in section 16.2.2.3.

16.2.4. SENSITIVITY ANALYSIS OF SECONDARY EFFICACY VARIABLES

For the key secondary endpoints, the following sensitivity analysis will be performed at Week 12.

Subgroup analysis as specified in section 7.5 of the SAP.

- ANCOVA analysis with average imputation, as described in section 16.2.2 of the SAP.
- ANCOVA analysis with MI, only considering baseline and Week 12 (for lung function parameters) in the imputation model, as described in section 16.1.2 and 16.1.3 of the SAP.
- ANCOVA analysis with MI using the range data method as described in section 16.2.2.3 for SGRQ total score and weekly mean total E-RS.
- Tipping point approach, as described in section 16.1.2 of the SAP.
- Analysis with MI method, as described in sections 16.2.2 and 16.2.3 of the SAP, based on PP population.

For FEV_1 key secondary endpoints (FEV_1 $AUC_{0\text{-}4h}$, peak FEV_1, morning trough FEV_1) additional sensitivity analysis will be performed:

- MMRM model with treatment, visit and treatment by visit as fixed effect; baseline as covariate; patient as random factor; unstructured covariance by visit. If the model does not converge a compound symmetry covariance structure will be used. Kenward-Roger method will be used to estimate the model degrees of freedom.weeks.

For weekly mean E-RS total score and SGRQ total score, additional analysis will be performed:

- For weekly mean E-RS total score at 6, 12 and 24 weeks, using ANCOVA approach, as described in section 16.2.3 of the SAP, all patients with baseline weekly mean = 0 will be excluded.
- For SQRG total score at 6, 12 and 24 weeks, using ANCOVA approach, as described in section 16.2.3.1 of the SAP, all patients with baseline assessment done after dosing time and date will be excluded.

16.3. OTHER EFFICACY

The other efficacy analyses will be performed for the mITT population.

- Moderate/severe COPD exacerbation frequency over 24 weeks.
- Time to first moderate/severe COPD exacerbation over 24 weeks.
- Study withdrawal before scheduled visit at 24 weeks.
- Change from baseline to post-baseline EQ-5D-5L at Week 12
- HRU over 24 weeks
- Change from baseline FEV_1 to average FEV_1 $AUC_{6\text{-}12h}$ at Week 12
- Ensifentrine concentrations following sparse PK sample collection at Weeks 6, 12 and 24
- Patient genotype/phenotype including but not limited to cytochrome P-450 (CYP)2C9 and CYP2D6 metabolic activity
- Interleukin (IL)-6, IL-8 and C-reactive protein at Weeks 12 and 24
- E-RS responder analysis
- Morning trough FEV_1 responder analysis

16.3.1. OTHER EFFICACY VARIABLES & DERIVATIONS

16.3.1.1. COPD exacerbation

COPD exacerbations are collected on the "COPD Exacerbation" page of the eCRF and severity will be derived separately using data collected in the eCRF and as per the criteria specified in section 11.6.1. of the study protocol.

Site must enter at least 2 major symptoms, or one major symptom and one minor symptom AND meet the severity criteria below, considered as a moderate or severe exacerbation of COPD.

The severity of the COPD exacerbation will be calculated as per the following:

Moderate: Worsening symptoms of COPD requiring a minimum of three days of treatment with oral/systemic corticosteroids and/ or antibiotics.

Severe: Worsening symptoms of COPD requiring in-patient hospitalization.

16.3.1.2. EQ-5D-5L

Quality of Life (QoL) was assessed using the EQ-5D-5L questionnaire. This questionnaire

[redacted]

consits of 5 domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression with 5 possible responses from 1 (no problem) to 5 (unable). The sixth item, referred to as a visual analogue scale (VAS) score, is an index score to self-rate health from 0 (worst) to 100 (best). Each of the 5 domains will be summed through weighing system into a health index. The health index and VAS score will be analysed and listed and 5 domains will be only listed. It is not possible to have missing items in the questionnaire, as the data are collected in an electronic tablet which doesn't allow patients to skip between items. The weighting system is described in APPENDIX 6 of the SAP.

16.3.1.3. HRU

HRU is measured by the following events: unscheduled visits to a physician office, visits to urgent care, visits to emergency department and hospitalizations for any cause and/or related to COPD and visits/contact due to COPD exacerbation. These will be recoded on the Log Form and "COPD Exacerbation" pages of the eCRF, respectively .

16.3.1.4. Genotype/phenotype

Genetics analysis is described in section 18 of the SAP.

16.3.1.5. Patient Perception Survey

At the follow-up contact each patient will fill in a survey on their perception of what drug they were on. Data recorded on "Patient Perception Survey" page of the eCRF will be listed and summarized by treatment group for the following categories:

- Patients who correctly guessed their drug
- Patients who incorrectly guessed their drug
- Patients who were unsure of their drug

16.3.1.6. FEV_1 $AUC_{6\text{-}12h}$

Average FEV_1 $AUC_{6\text{-}12h}$ is calculated as described in section 16.1.1.1 of the SAP.

16.3.1.7. E-RS total score responder

E-RS total score responder is defined as a decrease from baseline in the week mean total of E-RS score greater than or equal to 2.

16.3.1.8. Morning trough FEV_1 responder

Morning trough FEV_1 responder is defined as an increase from baseline in the Morning trough FEV_1 greater than or equal to 100 mL.

16.3.2. Missing Data Methods for Other Efficacy Variables

For EQ-5D-5L missing data will be imputed using imputation described in section 16.2.2.3 of the SAP and FEV_1 $AUC_{6\text{-}12h}$ missing data will be imputed using imputation described in section 16.2.2.1 of the SAP. Morning trough FEV_1 responder missing data will be handled as described in sections 16.2.2.2 of the SAP. E-RS total score responder missing data will be imputed similar to the SGRQ total score responder analysis as described in sections 16.2.2.3 of the SAP.

16.3.3. Analysis of Other Efficacy Variables

Change from baseline to average FEV_1 $AUC_{6\text{-}12h}$ will be analyzed using ANCOVA approach and missing data will be imputed using imputation, as described in sections 16.1.3 and 16.2.2.1 of the SAP, respectively.
Model assumptions will be tested and solved, if failed, as per section 16.1.3 of the SAP.

The number of moderate or severe COPD exacerbations will be analyzed using a negative binomial model adjusting for treatment, region, actual background medication strata and actual smoking strata, as well as using log study time (years) as an offset. For study time, Visit 5 will be taken into account for completer patients, and End of Study visit or last contact date for withdrawal patients. The treatment difference from the negative binomial model will be expressed as an annualized risk ratio. The data will also be summarized by treatment group over duration of the study period.
Time to first moderate or severe COPD exacerbation during the study period will be presented as per following:

- Primary approach: Analyzed using the log-rank test, stratified by region, actual background medication strata and actual smoking strata. Summary of number of patients with events and number of patients censored will be summarized. Outcome visualized using a Kaplan-Meier plot.
- Sensitivity analysis: Analyzed using Cox proportional hazards Regression model stratified by region, background medication strata and smoking strata. Patients without exacerbations will be censored at last day in the treatment period, including period of recording after possible treatment withdrawal. The treatment difference in the Cox model will be expressed as a hazard ratio.

Testing proportional hazard assumptions:

1. Check that the covariates are independent of each other through proc phreg in SAS software.
2. Check that the hazard (hazard ratio) is independent of time through log(-log(survival)) vs log(time) plot and an interaction test for treatment times log(time).

The health index and VAS score for EQ-5D-5L questionnaire will be analyzed using ANCOVA approach, as described in section 16.1.3 of the SAP, with data imputation described in section 16.2.2.3 of the SAP.

HRU over 24 weeks will be summarized for each event and for overall count.

Analysis for the genetics data is described in section 18 of the SAP.

Sensitivity analysis of subgroup analysis may be considered following results of the patient perception survey. The survey will be summarized to investigate if there are any signs of breeching of the blind related to the appearance of study medication.

Proportion of E-RS total score responders will be analyzed by means of a logistic regression model with fixed effects for treatment, region, actual background medication strata and actual smoking strata at baseline and baseline E-RS total score as covariate. Missing data will be imputed as described in sections 16.2.2.2 and 16.2.2.3.

Proportion of responders, with an improvement from baseline in Morning trough FEV_1 of 100 mL or more will be analyzed using a logistic regression model with fixed effects for treatment, region, actual background medication strata and actual smoking strata at baseline and baseline Morning trough FEV_1 as covariate. Missing data will be imputed as described in sections 16.2.2.2 and 16.2.2.3.

16.3.4. Sensitivity Analysis of Other Efficacy Variables

Sensitivity analysis with no data imputation, including only patients with data collected at the required visit while still on randomized treatment at scheduled visit, or at end of study visit within the visit window will be performed on the health index and VAS score for EQ-5D-5L questionnaire and analyzed using ANCOVA approach, as described in section 16.1.3 of the SAP.
Time to first moderate or severe COPD exacerbation will be analyzed using Cox proportional hazards Regression model as described in section 16.3.3.

16.4. EVALUATION INCLUDING EXCLUDED SITES

Site [redacted] was removed from the mITT. As a check of the impact of this exclusion, the following analyses will be performed in the mITT Extended dataset.

- Analysis of FEV_1 AUC_{0-12}
- Analysis of peak FEV_1
- Analysis of E-RS total score
- Analysis of SGRQ total score
- Analysis of morning trough FEV_1
- Responder analysis of SGRQ total score

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF set.
There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

17.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA central coding dictionary. The version of MedDRA to be used will be specified prior to database lock.
Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication. Laboratory or ECG findings from procedures or samples drawn prior to the first does of study medication that are assessed/overread after randomization will be considered pre-treatment.
In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified by the worst case; i.e. treatment-emergent.

See Appendix 2 for handling of partial dates for AEs.

An overall summary of number of patients within each of the categories described in the sub-section below, will be provided as specified in the shells. In addition, the number of patients with each of the following AE events will be presented by SOC and PT and summarized by treatment group and different period (i.e. Treatment period, Follow-up and Overall):

- TEAE
- TEAEs causally related to study medication

- Serious TEAEs
- TEAEs with an outcome of death
- TEAEs leading to discontinuation of blinded study medication
- TEAEs leading to withdrawal from study (TEAEs with a diagnosis of COVID-19, TEAEs with no diagnosis of COVID-19)
- TEAEs by maximum severity

AEs will be identified by using the "Adverse Events" page of the eCRF. Listings will include TEAEs and Non-TEAEs.

Treatment period is defined as the period from the date and time of first dose up to the date and time of last dose.
Follow-up is defined as the period from after the date and time of last dose up to the last date recorded on the study.

17.1.1. ALL TEAEs

Incidence of TEAEs will be presented by SOC and PT and broken down further by maximum severity and relationship to study medication.

17.1.1.1. Severity

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If patient reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

17.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as "unknown", "unrelated", "unlikely to be related", "possibly related" and "probably related" (increasing probability of relationship). A "related" TEAE is defined as a TEAE with a relationship to study medication as "possibly related" or "probably related" to study medication. TEAEs with a missing relationship to study medication will be regarded as "probably related" to study medication. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

17.1.2. TEAEs LEADING TO DISCONTINUATION OF STUDY MEDICATION

TEAEs leading to discontinuation of study medication are AEs recorded as "Study Treatment Permanently Discontinued" on the "Adverse Events" page of the eCRF.

For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

17.1.3. SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are those events recorded as ”Serious” on the “Adverse Events” page of the eCRF. A summary of serious TEAEs by SOC and PT and by treatment group and different period (i.e. Treatment period, Follow-up and Overall) will be prepared.

17.1.4. ADVERSE EVENTS LEADING TO DEATH

TEAEs leading to Death are those events which are recorded as ”Fatal” on the “Adverse Events” page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

17.2. LABORATORY EVALUATIONS

Results from the central laboratory (or local laboratory where this is required) will be included in the reporting of this study for chemistry, hematology and viral serology. A list of laboratory assessments to be included in the outputs is included in the Appendix 3 of the study protocol. Presentations of all laboratory tests will use standard international (SI) units. However, certain laboratory tests will also be presenting using US units, including liver tests.
The handling of re-test and unscheduled measurements is detailed in section 6.4 of the SAP.

The following summaries will be provided for chemistry and hematology data:

- Actual and change from baseline by visit (for quantitative measurements)
- Incidence of abnormal values according to normal range criteria
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements)
- Shift from baseline according to markedly abnormal criteria (for quantitative measurements and categorical measurements)
- Listing of patients meeting markedly abnormal criteria

Viral serology, COVID-19 sample, chemistry and hematology will be listed.

17.2.1. Laboratory Reference Ranges and Clinically Significant Abnormal Criteria

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

In addition to the high and low quantitative laboratory assignments (as identified by means of the laboratory reference ranges), clinically significant abnormal quantitative chemistry laboratory assessments will also be identified in accordance with the predefined markedly abnormal criteria as presented in Table 4.

If ULN or LLN have "≤X" or "≥X" then "X" will be used for analysis and "≤X" or "≥X" will only be used in listings.

Table 4: Clinically Significant abnormal criteria for laboratory parameters

Parameter	Clinically Significant Abnormally High Criteria
Alanine Aminotransferase (ALT)	> 3 times Upper Limit of Normal Range
Alkaline Phosphatase	> 3 times Upper Limit of Normal Range
Aspartate Aminotransferase (AST)	> 3 times Upper Limit of Normal Range
Creatinine	>221 µmol/L
Gamma Glutamyltransferase (GGT)	> 3 times Upper Limit of Normal Range
Total Bilirubin	> 3 times Upper Limit of Normal Range

17.3. ECG Evaluations

Results from the central Electrocardiogram (ECG) Reading Centre will be included in the reporting of this study.
The following ECG parameters will be reported for this study:

- PR Interval (msec)

- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec)
- QTcB Interval (msec)
- Heart Rate (beats per minute [bpm])
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (ANCS)
    - Abnormal, Clinically Significant (ACS)

On Day 1, prior to dosing, triplicate ECGs must be performed. Triplicate results will be used in the summaries by taking an average of the 3 results. The average of the 3 results will be the baseline. Baseline for the investigator's judgement will be the mode judgment of the 3 results. In the case of multiple modes, the mode with the worst-case judgment (Normal<ANCS<ACS) will be used as baseline.
If only 2 ECG measurements instead of triplicate on Day 1 pre-dose, take average of the two; if only 1 measurement then this will be the baseline.
The handling of re-test and unscheduled measurements is detailed in section 6.3of the SAP.

If there were more measurements on a scheduled visit, choose measurement as follows:

1. Choose first triplicate, if more than one done.
2. If done on Day 1, ensure you choose measurement that it is prior to dosing.
3. If there are more than 1 ECG measurements, choose the scheduled one where interpretation of the measurement from the vendor data is not "UNABLE TO EVALUATE" .
    a. If pre-dose/post-dose and interpretation of the measurement from the vendor data is "UNABLE TO EVALUATE" and no further pre-dose/post-dose unscheduled visits on the same day, respectively – set to missing
    b. If pre-dose/post-dose and interpretation of the measurement from the vendor data is "UNABLE TO EVALUATE" and there is another unscheduled pre-dose/post-dose – choose next unscheduled visit on the same day

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)
- Shift table representing changes from Normal, ANCS and ACS, using Investigator's judgement
- Incidence of markedly abnormal criteria

- Listing of patients meeting markedly abnormal criteria

17.3.1. ECG MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria:

- Absolute values for QT interval, QTcB interval and QTcF interval will be classified as:
  - > 450 msec
  - > 480 msec
  - > 500 msec
- Change from Baseline for QT interval, QTcB interval and QTcF will be classified as:
  - >30 msec increase from baseline
  - >60 msec increase from baseline

17.4. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Supine Systolic Blood Pressure (mmHg)
- Supine Diastolic Blood Pressure (mmHg)
- Supine Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (ºC)
- Body weight (kg)
- Height (cm)
- BMI (kg/m^2)

The following summaries will be provided for vital signs data (excluding respiratory rate, temperature, body weight, height and BMI):

- Actual and change from baseline by visit
- Incidence of markedly abnormal values
- Shift from baseline according to markedly abnormal criteria
- Listing of patients meeting markedly abnormal criteria

Respiratory rate, temperature, body weight, height and BMI will be listed.

17.4.1. VITAL SIGNS MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the predefined markedly abnormal criteria found in Table 5.

Markedly Abnormal Post-Baseline Vital Sigs

Variable	Unit	Abnormally Low	Abnormally High
SBP	mmHg	- A decrease from Baseline of ≥40 - Value ≤90	- An increase from Baseline of ≥40 - Value ≥180
DBP	mmHg	- A decrease from Baseline of ≥20 - Value ≤50	- An increase from Baseline of ≥20 - Value ≥105
Pulse rate	Bpm	- A decrease from Baseline of ≥30 - Value ≤50	- An increase from Baseline of ≥30 - Value ≥110

17.5. COVID-19

From study initiation until 5Nov2021, patients with positive COVID-19 test indicating an active COVID-19 infection were withdrawn from the study.

A protocol clarification letter dated 5Nov2021 clarified that active infection includes known symptoms of COVID-19.

A protocol clarification letter dated 21Apr2022 clarified that active infection includes known lower respiratory symptoms of COVID-19.

Patients with discontinued due to COVID-19 will be summarized in the disposition table. Data collected on the "COVID-19 Visit Impact" eCRF page will be summarized by visit. Data on the optional COVID-19 testing will be listed.

17.6. PNEUMONIA

Pneumonia details recorded in the "Pneumonia" page of the eCRF will be listed.

17.7. EVALUATION INCLUDING EXCLUDED SITES

The following analyses will be performed on the Extended Safety Set:

- Summary of TEAEs
- TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Markedly abnormal values for selected chemistry parameters
- Markedly abnormal values for vital signs
- Markedly abnormal values for ECG parameters

18. GENETIC ANALYSIS

Genotyping analyses (CYP2C9 and CYP2D6 phenotypes) will be completed as exploratory analysis by the sponsor and are not covered in this SAP.

19. BIOMARKER ANALYSIS

Assessment of Biomarkers (IL-6, IL-8 and C-Reactive Protein [CRP]) will be analyzed for the mITT using ANCOVA approach, as described in section 16.1.3 of the SAP at Weeks 12 and 24. Log transformation will be done on the data for the ANCOVA analysis. Values that are below limit of quantitation (LOQ) will be treated as LOQ/2 for analyses and summaries. Missing data will not be imputed. Biomarker data are blinded until after DBL.

20. PHARMACOKINETIC ANALYSIS

20.1. DEVIATIONS RELATED TO PK

Changes to the procedures or events, which may impact the quality of the pharmacokinetic (PK) data, will be considered important PDs for the purpose of inclusion of the affected results in the concentration summary. These changes or events will include any circumstances that will alter the evaluation of the PK. Examples include, but may not be limited to, an incomplete/inaccurate dose of ensifentrine inhaled and/or a prolonged interruption of nebulization (example due to prolonged coughing, etc.), sample handling/shipment/processing errors that lead to inaccurate bioanalytical results, and/or noncompliance in ensifentrine administration (inaccurate and/or incomplete dose administration). Interruption of nebulization

or spillage resulting in loss of more than 50% of dose will be evaluated on case-by-case basis to determine whether exclusion of ensifentrine results from analysis is warranted. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered significant PDs. A common example of a non-significant PDs is a missed blood sample.

A general rule for handling of time deviations for the descriptive summary of the concentration data is provided below:

- If the most recent 2 prior doses were missed, then the pre-dose and postdose concentrations for the affected visit will not be included in the concentration summary.
- If the most recent prior dose was administered less than 6 hours prior or more than 18 hours prior to collection of the scheduled pre-dose sample (ie, the pre-dose sample is not collected within the window of 6 to 18 hours prior to the end of the inhalation of the last dose), the pre-dose concentration will not be summarized. Any post-dose concentrations scheduled for the affected visit will be included in the summaries.
- Samples scheduled to be paired with the 1.5-hour ECG collection will be summarized if they were collected within the window of ± 0.5 hours (relative to end of the inhalation).
- Pre-dose samples collected after start of the inhalation will be excluded from the summaries.
- Samples collected outside the allowable window specified in the protocol will not be summarized.
- ET/withdrawal results will be listed only as long as the patient has received at least 1 dose of ensifentrine.

Note: Sample collection records will be reviewed before or during final analysis to determine the extend loss of data records based on the above specifications. If the loss of records is considered to be unacceptable, the above windowing may be modified (widened) for inclusion of additional data in the concentration summary. Any decision to widen the acceptance criteria will be documented in the clinical study report.

A listing with patients or concentration results excluded from the summary statistics and the reasons for exclusion will be provided.

20.2. PHARMACOKINETICS DRUG CONCENTRATIONS IN PLASMA

Pharmacokinetic concentration outputs will be based on the PK set. Pharmacokinetic data will be blinded until after DBL. The observed drug concentrations will be listed and summarized by site (even / odd), as per schedule of Table 9 in the Protocol, and for each sampling time point by visit, using descriptive statistics (including N [sample size], n [available data], n < below lower limit of quantitation [BLQ], mean, SD, coefficient of variation [CV%], median, minimum, and maximum. Concentrations that are BLQ will be treated as zero for concentration

summaries. There will be no imputation of missing data.

A listing of PK blood sample collection times, derived sampling time deviations, and actual sample time will be also provided. Blood samples are to be collected as per schedule of Table 9 in Protocol. All PK concentrations will be listed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimal places the data carry.

For the reporting of descriptive statistics of PK concentrations, the mean and SD will be presented to 1 digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data. CV% will always be reported to 1 decimal place. A minimum of n=3 is required for all descriptive statistics to be generated. If n is less than 3, only N, n, minimum, and maximum will be reported.

The concentration listing and summary will be described as appropriate in the clinical study report.

20.3. POPULATION PK ANALYSIS

The strategy for the population PK analysis and any related exposure-response modeling utilizing the ensifentrine concentration and response data from this study will be outlined separately in the modeling data analysis plan prepared by Verona Pharma/Designee.

21. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments
- Physical Examinations, as it is not collected within eCRF

These domains and/or variables will not be summarized or presented, but if collected will be available in the clinical study database, SDTM and/or ADaM datasets.

22. REFERENCES

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Ratitch B., O. M. (2014). *Clinical Trials with Missing Data: A Guide for Practitioners.* John Wiley & Sons, Ltd.

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APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in the given order:

Treatment Group	For Tables, Listings and Graphs
Ensifentrine	Ensifentrine
Placebo	Placebo
Not Randomized	Not Randomized

DECIMAL PLACES

The decimal places for this study will use the following rules, unless otherwise stated.
Value = x dp
Mean = x+1 dp
Standard Deviation = x+2 dp
Median = x+1 dp
Q1/Q3 = x+1 dp
Minimum/Maximum = x dp
CI = x+1 dp

In case a variable has values with infinite decimal places, the following rules will be used:
Value = 1 dp
Mean = 2 dp
Standard Deviation = 3 dp
Median = 2 dp
Q1/Q3 = 2 dp
Minimum/Maximum = 1 dp

CI = 2 dp

For spirometry data we will present outputs with decimal places for value as follows:

- Values in liters = 3 dp, i.e. mean/median/Q1/Q3/CI in liters = 4 dp, standard deviation = 5 dp and minimum/maximum = 3 dp.
- Values in milliliters = 0 dp, i.e. mean/median/Q1/Q3/CI in liters = 1 dp, standard deviation = 2 dp and minimum/maximum = 0 dp.
- Percentage values = 1 dp, i.e. mean/median/Q1/Q3/CI in liters = 2 dp, standard deviation = 3 dp and minimum/maximum = 1 dp.

P-values will be presented to 4dp.

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	**Short Name**
Screening	Screening
day 1	day 1
week 6	week 6
week 12	week 12
week 18	week 18
week 24	week 24
Follow-up	Follow-up

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized treatment group (or treatment received if it's a safety output), first by active dose and then placebo,
- Center-patient ID,
- Date and time (where applicable),
- For listings where non-randomized patients are included, these will appear in a category

after the randomized treatment groups labeled ‘Not Randomized’.

TABLES

All tables presenting multiple events that map to a SOC and PT will be counted only once, per unique patient, for incidence counts. Events will be presented in descending frequency of SOC and PT (unless otherwise indicated in the shells).

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study med start date OR Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

[redacted]

ALGORITHM FOR PRIOR/ PRIOR CONCOMITANT / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date < study med start, assign as prior concomitant If stop date >= study med start date and (start date > study med start or start date <= end of treatment), assign as concomitant If start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date < study med start, assign as prior concomitant If stop date >= study med start date and (start date > study med start or start date <= end of treatment), assign as concomitant If start date > end of treatment, assign as post study
	Missing	If stop date is missing could never be assumed a prior medication If stop date >= study med start date and start date < study med start, assign as prior concomitant If stop date >= study med start date and (start date > study med start or start date <= end of treatment), assign as concomitant If start date > end of treatment, assign as post study

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date < study med start, assign as prior concomitant If stop date >= study med start date and (start date > study med start or start date <= end of treatment), assign as concomitant If start date > end of treatment, assign as post study
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date < study med start, assign as prior concomitant If stop date >= study med start date and (start date > study med start or start date <= end of treatment), assign as concomitant If start date > end of treatment, assign as post study
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If stop date >= study med start date and start date < study med start, assign as prior concomitant If stop date >= study med start date and (start date > study med start or start date <= end of treatment), assign as concomitant If start date > end of treatment, assign as post study

[redacted]

START DATE	STOP DATE	ACTION
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'prior concomitant' and 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'prior concomitant' and 'post treatment'
	Missing	Assign as concomitant

ALGORITHM FOR CONCOMITANT ILLNESSES:

START DATE	STOP DATE	ACTION
Known	Known	If stop date > date of first treatment dose and start date <= date of first treatment dose, assign as concomitant illness
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date > date of first treatment dose and start date <= date of first treatment dose, assign as concomitant illness
	Missing	If stop date is missing then assume concomitant illness
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date > date of first treatment dose and start date <= date of first treatment dose, assign as concomitant illness
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date > date of first treatment dose and start date <= date of first treatment dose, assign as concomitant illness
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing then assume concomitant illness
Missing	Known	If stop date > date of first treatment dose, assign as concomitant illness

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date > date of first treatment dose, assign as concomitant illness
	Missing	If stop date is missing then assume concomitant illness

APPENDIX 3. ANNOTATED EXACT FOR RAW SCORE ASSIGNMENT

1. Did your chest feel congested today?	0.Not at all
	1.Slightly
	2.Moderately
	3.Severely
	4.Extremely
2. How often did you cough today?	0.Not at all
	1.Rarely
	2.Occasionally
	3.Frequently
	4.Almost constantly
3. How much mucus (phlegm) did you bring up when coughing today?	0.None at all
	1.A little
	1.Some
	2.A great deal
	3.A very great deal
4. How difficult was it to bring up mucus (phlegm) today?	0.Not at all
	1.Slightly
	2.Moderately
	3.Quite a bit
	4.Extremely
5. Did you have chest discomfort today?	0.Not at all
	1.Slight
	2.Moderate
	3.Severe
	4.Extreme
6. Did your chest feel tight today?	0.Not at all
	1.Slightly
	2.Moderately
	3.Severely
	4.Extremely
7. Were you breathless today?	0.Not at all
	1.Slightly
	2.Moderately
	3.Severely
	4.Extremely

[redacted]

8.Describe how breathless you were today	0.Unaware of breathlessness
	1.Breathless during strenuous activity
	2.Breathless during light activity
	3.Breathless when washing or dressing
	3.Present when resting
9. Were you short of breath today when performing your usual personal care activities like washing or dressing?	0.Not at all
	1.Slightly
	2.Moderately
	3.Severely
	3.Extremely
	4.Too breathless to do these
10. Were you short of breath today when performing your usual indoor activities like cleaning or household work?	0.Not at all
	1.Slightly
	2.Moderately
	3.Severely
	3.Extremely
	3.Too breathless to do these
11. Were you short of breath today when performing your usual activities outside the home such as yard work or errands?	0.Not at all
	1.Slightly
	2.Moderately
	3.Severely
	3.Extremely
	3.Too breathless to do these
12. Were you tired or weak today?	0.Not at all
	1.Slightly
	2.Moderately
	3.Severely
	4.Extremely
13. Last night, was your sleep disturbed?	0.Not at all
	1.Slightly
	2.Moderately
	3.Severely
	4.Extremely
14. How scared or worried were you about your lung problems today?	0.Not at all
	1.Slightly
	2.Moderately
	3.Severely

	3.Extremely

APPENDIX 4. RAW SUMMED SCORE TO SCALE CONVERSION TABLE FOR EXACT TOTAL SCORE

Raw Summed Score	EXACT Total Score	Raw Summed Score	EXACT Total Score
0	0	26	50
1	8	27	51
2	13	28	52
3	17	29	53
4	20	30	54
5	23	31	55
6	25	32	57
7	27	33	58
8	28	34	59
9	30	35	60
10	31	36	61
11	33	37	63
12	34	38	64
13	36	39	65
14	37	40	67
15	38	41	68
16	39	42	70
17	40	43	72
18	41	44	73
19	42	45	75
20	43	46	77
21	44	47	80
22	46	48	83
23	47	49	87
24	48	50	92
25	49	51	100

APPENDIX 5. SGRQ ITEM WEIGHTS

Question	Answers	Weight
Part 1		
Question 1: Over the past 4 weeks, I have coughed		
	Almost every day	80.6
	Several days a week	63.2
	A few days a month	29.3
	Only with respiratory infections	28.1
	Not at all	0.0
Question 2: Over the past 4 weeks, I have brought up phlegm (sputum)		
	Almost every day	76.8
	Several days a week	60.0
	A few days a month	34.0
	Only with respiratory infections	30.2
	Not at all	0.0
Question 3: Over the past 4 weeks, I have shortness of breath		
	Almost every day	87.2
	Several days a week	71.4
	A few days a month	43.7
	Only with respiratory infections	35.7
	Not at all	0.0
Question 4: Over the past 4 weeks, I have wheezing attacks		
	Almost every day	86.2
	Several days a week	71.0
	A few days a month	45.6
	Only with respiratory infections	36.4
	Not at all	0.0
Question 5: How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?		
	More than 3 times	86.7
	3 times	73.5
	2 times	60.3
	1 time	44.2
	None of the time	0.0
Question 6: How long did the worst respiratory attack last?		
	A week or more	89.7
	3 or more days	73.5

(Go to Question 7 if you did not have a severe attack)	1 or 2 days	58.8
	Less than a day	41.9
Question 7: Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?		
	No good days	93.3
	1 or 2 good days	76.6
	3 or 4 good days	61.5
	Nearly every day was good	15.4
	Every day was good	0.0
Question 8: If youwheeze, is it worse when you get up in the morning?		
	No	0.0
	Yes	62.0
Part 2		
Question 9: How would you describe your respiratory condition?		
	The most important problem I have	83.2
	Causes me quite a lot of problems	82.5
	Causes me a few problems	34.6
	Causes no problem	0.0
Question 10: If you ever held a job		
	My respiratory problems made me stop working altogether	88.9
	My respiratory problems interfere with my job or made me change my job	77.6
	My respiratory problems do not affect my job	0.0
Question 11: Questions about what activities usually make you short of breath these days		
	Sitting or lying still	90.6
	Washing or dressing yourself	82.8
	Walking around the house	80.2
	Walking outside on level ground	81.4
	Walking up a flight of stairs	76.1
	Walking up hills	75.1
	Playing sports or other physical activities	72.1
Question 12: More questions about your cough and shortness of breath these days		
	Coughing hurts	81.1
	Coughing makes me tired	79.1

	I am short of breath when I talk	84.5
	I am short of breath when I bend over	76.8
	My coughing or breathing disturbs my sleep	87.9
	I get exhausted easily	84.0
Question 13: Questions about other effects your respiratory problems may have on you these days		
	My cough or breathing is embarrassing in public	74.1
	My respiratory problems are a nuisance to my family, friends or neighbors	79.1
	I get afraid or panic when I cannot catch my breath	87.7
	I feel that I am not in control of my respiratory problems	90.1
	I do not expect my respiratory problems to get any better	82.3
	I have become frail or an invalid because of my respiratory problems	89.9
	Exercise is not safe for me	75.7
	Everything seems too much of an effort	84.5
Question 14: Questions about your respiratory treatment		
	My treatment does not help me very much	88.2
	I get embarrassed using my medication in public	53.9
	I have unpleasant side effects from my medication	81.1
	My treatment interferes with my life a lot	70.3
Question 15: Questions about how activities may be affected by your respiratory problems		
	I take a long time to get washed or dressed	74.2
	I cannot take a bath or shower, or I take a long time	81.0

	I walk more slowly than other people, or I stop to rest	71.7
	Jobs such as housework take a long time, or I have to stop to rest	70.6
	If I walk up one flight of stairs, I have to go slowly or stop	71.6
	If I hurry or walk fast, I have to stop or slow down	72.3
	My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, play bowls or play golf	74.5
	My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	71.4
	My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	63.5
Question 16: We would like to know how your respiratory problems usually affect your daily life		
	I cannot play sports or other physical activities	64.8
	I cannot go out for entertainment or recreation	79.8
	I cannot go out of the house to do the shopping	81.0
	I cannot do household chores	79.1
	I cannot move far from my bed or chair	94.0
Question 17: Tick the statement which you think best describes how your respiratory problems affect you		
	It does not stop me from doing anything I would like to do	0.0

	It stops me from doing one or two things I would like to do	42.0
	It stops me from doing most of the things I would like to do	84.2
	It stops me from doing everything I would like to do	96.7

APPENDIX 6. EQ-5D-5L WEIGHTS

To account for this study collecting data in multiple countries, different EQ-5D-5L weights will be used depending on the country, as presented in Table 5.

Table 5: EQ-5D-5L geographical region categorisation

Countries	Version used
Eastern Europe: Bulgaria, Hungary, Poland, Slovakia, Estonia	Poland (EQ-VT v2.0)
Western Europe: Belgium, Denmark, Spain	England (EQ-VT v1.0)
North America: US, Canada	US (EQ-VT v2.0)

Data collected from questionnaire will be numbered, as presented in Table 6.

Table 6: EQ-5D-5L data collection

Variable name	Mobility	Self-care	Usual Activities	Pain/ Discomfort	Anxiety/ Depression	Health score	VAS
Variable score range	1-5	1-5	1-5	1-5	1-5	5-digit code for EQ-5D-5L	0-100
Data row example	2	3	1	1	1	23111	83

The health score is a combination of the scores for the 5 questions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) in the order they are collected, as shown in the data row example in Table 6.

POLAND

The health index is calculated by first summing all weights related to the scores from the questionnaire and subtracting it from 1, i.e. for data row example in Table 6 the health index would be 0.928. Weights related to each score are presented in Table 7.

Table 7: Weights

Variable	Score	Weights
Mobility	1	0
	2	0.025
	3	0.034
	4	0.126
	5	0.314
Self-care	1	0
	2	0.031
	3	0.047
	4	0.111
	5	0.264
Usual Activities	1	0
	2	0.023
	3	0.040
	4	0.097
	5	0.205
Pain/discomfort	1	0
	2	0.030
	3	0.050
	4	0.261
	5	0.575

Anxiety/ depression	1	0
	2	0.018
	3	0.029
	4	0.108
	5	0.232

ENGLAND

The health index is calculated by first summing all weights related to the scores from the questionnaire and subtracting it from 1, i.e. for data row example in Table 6 the health index would be 0.879. Weights related to each score are presented in Table 8.

Table 8: Weights

Variable	Score	Weights
Mobility	1	0
	2	0.058
	3	0.076
	4	0.207
	5	0.274
Self-care	1	0
	2	0.050
	3	0.080
	4	0.164
	5	0.203
Usual Activities	1	0
	2	0.050

	3	0.063
	4	0.162
	5	0184
Pain/discomfort	1	0
	2	0.063
	3	0.084
	4	0.276
	5	0.335
Anxiety/ depression	1	0
	2	0.078
	3	0.104
	4	0.285
	5	0.289

US

The health index is calculated by first summing all weights related to the scores from the questionnaire and subtracting it from 1, i.e. for data row example in Table 6 the health index would be 0.797. Weights related to each score are presented in Table 9.

Table 9: Weights

Variable	Score	Weights
Mobility	1	0
	2	0.096
	3	0.122
	4	0.237

	5	0.322
Self-care	1	0
	2	0.089
	3	0.107
	4	0.220
	5	0.261
Usual Activities	1	0
	2	0.068
	3	0.101
	4	0.255
	5	0.255
Pain/discomfort	1	0
	2	0.060
	3	0.098
	4	0.318
	5	0.414
Anxiety/ depression	1	0
	2	0.057
	3	0.123
	4	0.299
	5	0.321