STATISTICAL ANALYSIS PLAN

SUN101-402

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 2-WAY CROSSOVER STUDY OF THE EFFECT OF A SINGLE DOSE OF GLYCOPYRROLATE INHALATION SOLUTION (GIS) ON LUNG HYPERINFLATION IN SUBJECTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V3.0 (Dated 06May2020) for Protocol SUN101-402 Version 1.0.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AUC	Area under the curve
BDR	Blinded data review
BMI	Body mass index
CFB	Change from baseline
CI	Confidence Interval
cm	centimeter
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EFF	Efficacy
ENR	Enrolled
EOS	End of study
FEV1	Forced expiratory volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
GIS	Glycopyrrolate inhalation solution
IC	Inspiratory capacity
ICF	Informed consent form
IPD	Important protocol deviation
kg	kilogram
LS	Least Squares
m	meter
MAR	Missing at random
Mcg	Microgram
MCMC	Markov chain Monte Carlo

MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
mmHg	Millimeters of Mercury
mMRC	Modified Medical Research Council Dyspnea Scale
MNAR	Missing not at random
PIS	Placebo inhalation solution
PMM	Pattern-mixture model
PT	Preferred Term
Q1	Quartile 1
Q3	Quartile 3
RV	Residual Volume
Raw	Airway resistance
RND	Randomized
SAP	Statistical Analysis Plan
SD	Standard deviation
SAE	Serious Adverse Event
SAF	Safety
SCR	Screened
SGRQ	St. George's Respiratory Questionnaire
SOC	System organ class
SOP	Standard operating procedure
sRaw	Specific airway resistance
TLC	Total lung capacity
WHO-DD	World Health Organization Drug Dictionary

2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol SUN101-402 V1.00 07Aug2019. 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 1.0, dated 07Aug2019.

3. STUDY OBJECTIVES

3.1. PRIMARY EFFICACY OBJECTIVE

The primary objective is to compare the efficacy of Glycopyrrolate Inhalation Solution (GIS) versus Placebo Inhalation Solution (PIS) on lung hyperinflation following a single dose, as measured by residual volume (RV) at 6 hours postdose.

3.2. OTHER EFFICACY OBJECTIVE

The other efficacy objective is to evaluate the effect of a single dose of GIS versus PIS on objective measures of lung function.

3.3. EXPLORATORY OBJECTIVES

The exploratory objective is to evaluate the feasibility of using the accelerateIQ System (ie, the VitalPatch® Biosensor and accelerateIQ Platform).

3.4. STUDY ENDPOINTS

3.4.1. PRIMARY EFFICACY ENDPOINT

- Change from baseline in RV at 6 hours postdose

3.4.2. OTHER EFFICACY ENDPOINTS

- Standardized change from baseline in RV area under the curve from time 0 to 3 hours postdose (AUC0-3h), RV area under the curve from time 0 to 4 hours postdose (AUC0-4h) and RV area under the curve from time 0 to 6 hours postdose (AUC0-6h)
- Change from baseline in expiratory reserve volume (ERV) at 6 hours postdose
- Standardized change from baseline in ERV AUC0-3h, AUC0-4h and AUC0-6h
- Change from baseline in inspiratory capacity (IC) at 6 hours postdose
- Standardized change from baseline in IC AUC0-3h, AUC0-4h and AUC0-6h
- Change from baseline in functional residual capacity (FRC) at 6 hours postdose
- Standardized change from baseline in FRC AUC0-3h, AUC0-4h and AUC0-6h
- Change from baseline in total lung capacity (TLC) at 6 hours postdose
- Standardized change from baseline in TLC AUC0-3h, AUC0-4 h and AUC0-6h
- Change from baseline in specific airway resistance (sRaw) at 6 hours postdose
- Standardized change from baseline in specific Airway Resistance (sRaw) AUC0-3h, AUC0-4h and AUC0-6h
- Change from baseline in airway resistance (Raw) at 6 hours postdose
- Standardized change from baseline in Raw AUC0-3h, AUC0-4h and AUC0-6h
- Change from baseline in RV, ERV, IC, FRC, TLC, sRaw, and Raw at 1, 2, 3, and 4 hours postdose
- Change from baseline in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) at 6 hours postdose

3.4.3. SAFETY ENDPOINTS

- Incidence of adverse events, serious adverse events, and adverse events leading to discontinuation

3.4.4. EXPLORATORY ENDPOINTS

- Vital sign data collected at clinic visits and data collected using the accelerateIQ System

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

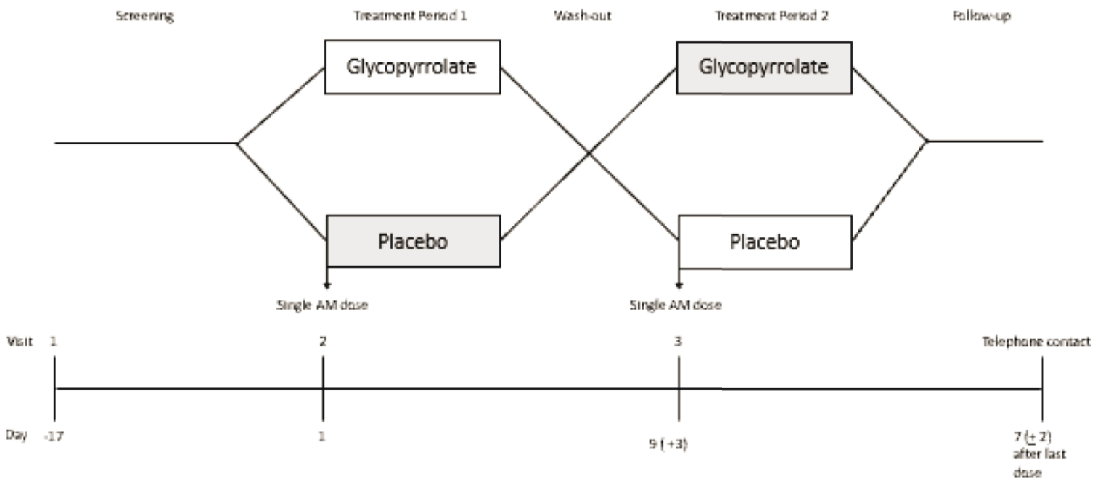
This is a single center, randomized, double-blind, placebo-controlled, single-dose 2-way crossover study in approximately 20 adult subjects ≥ 40 years of age with COPD. The study is designed to evaluate the effect of a single dose of GIS on lung hyperinflation. The two study treatments, both administered using the Magnair device are:

- GIS 25 mcg
- PIS

The study will consist of a Screening period, a randomized 2-way cross-over treatment period during which subjects will receive two single-doses each separated by a 7-day washout period, and a follow-up 7 (± 2) days after the last study drug dose.

A study schematic is provided in Figure 1, and detailed descriptions and timing of assessments is provided in Section 11 of the protocol.

Figure 1: Study Schematic



GIS = Glycopyrrolate Inhalation Solution

PIS = Placebo Inhalation Solution

It could be seen that treatment period 1 happens on Day 1 and treatment period 2/End of Study (EOS) happens on Day 9(+3). Details of the design at each visit can be found in Section 7.1 of the protocol.

4.2. METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

The randomization schedule, a sequential list consisting of the randomization numbers and their corresponding treatment sequence assignment, will be generated by a non-study biostatistician according to the process defined by the Sunovion/IQVIA's standard operating procedure (SOP).

Once a subject is deemed eligible to be randomized at Day 1 / Visit 2 and prior to dosing, all eligible subjects will be given a randomization number by the unblinded clinical staff member that assigns them to one of the two treatment sequences. Subjects will be randomized to one of the two following treatment sequences in a 1:1 ratio:

- Treatment sequence A→B (10 subjects): Single dose of GIS 25 mcg (Treatment A) to matching PIS (Treatment B).
- Treatment sequence B→A (10 subjects): Matching PIS (Treatment B) to single dose

of GIS 25 mcg (Treatment A).

Between each treatment sequence, subjects will undergo a 7-day washout period before returning to the clinic for the corresponding next treatment.

Randomization numbers will be assigned sequentially in the order the subject becomes eligible to participate in the study. Once a randomization number is assigned, it cannot be reused.

4.3. BLINDING

This is a double-blind study.

During the conduct of the study, in order to maintain the blind during the time of study drug administration, up until the analysis is conducted, an unblinded clinical staff member will perform the randomization and prepare and administer the study drug according to the randomization schedule. The unblinded study personnel will not perform any other blinded study procedures. All study drugs will be dispensed according to the randomization schedule to be supplied by Sunovion's representative, using a written study drug dispensing procedure that will assure that subjects remain blinded to the treatment being administered.

An unblinded clinical staff member will prepare and quality check each dose for each subject as instructed in the pharmacy manual according to the randomization schedule and other applicable local regulations as set forth in the protocol.

Subjects, Investigator staff, persons performing the assessments, clinical operations personnel, data analysts, and personnel at the laboratory will remain blinded to the identity of the treatment from the time of randomization until database lock and unblinding, using the following method: randomization data are kept strictly confidential (eg, sealed envelopes kept in a locked filing cabinet or placed in a safe at the study center and the randomization schedule created by the randomization administrator are kept in a secure location with restricted access) until the time of unblinding, and will not be accessible by anyone else involved in the treatment study with the exception of the Sunovion's clinical trials materials manager.

For emergency unblinding purposes, the Investigator will be provided with a sealed envelope for each subject. Inside, this envelope will contain information about the investigational product given to the subject according to the treatment schedule. The envelope may only be opened in the case of emergency when knowledge of the treatment is needed to treat the subject. In the case of unblinding, the Investigator is required to withdraw the subject from further study participation. These individual subject envelopes should be stored in a secure location and returned to the Sunovion/IQVIA, at the end of study.

4.4. DETERMINATION OF SAMPLE SIZE

The evaluable sample size for this study was determined by a two-sample t-test (cross-over ANOVA) using nQuery version 4.0 (nQuery + nTerim version 4.0, Statistical Solutions, Cork, Ireland). A sample size of 10 evaluable subjects per treatment sequence (20 subjects in total), assuming a common standard deviation (SD) of 0.4 L, a mean difference of -0.3 L in change from baseline in RV (single dose of GIS compared to PIS), with a one-sided alpha of 0.025, will give a power of 88%. Discontinued subjects will not be replaced. At the Sunovion's discretion, additional subjects may be enrolled in an effort to achieve at least 20 completers.

4.5. CHANGES IN THE CONDUCT OF THE STUDY

The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sunovion and the IRB, except where necessary to eliminate an apparent immediate hazard to a study subject.

4.6. SCHEDULE OF EVENTS

Schedule of events can be found in Table 2 of the protocol.

4.7. CHANGES TO ANALYSIS FROM PROTOCOL

The modified intent-to-treat (mITT) population from the protocol will be renamed as the efficacy (EFF) population due to possible IPD exclusions, including consideration of rescue medication use, from this population.

RV, IC, FRC, TLC, sRaw, Raw area under the curve from time 0 to 3 hours postdose (AUC0-3h), ERV AUC0-3h, ERV AUC0-4h, ERV AUC0-6h, change from baseline in ERV at 1, 2, 3, 4 and 6 hours postdose, and change from baseline in FVC at 6 hours postdose will be added for analysis.

No prior medication will be summarized. Only a listing will be provided.

Laboratory test and ECG results are only kept at site as source data and not collected on CRF. In general, laboratory and ECG evaluations will be conducted during the Screening visit to determine eligibility. Any clinically significant abnormality findings at Screening prior to the Placebo training dose, was to be recorded as medical history and any new, worsening clinically significant abnormality from the administration of the Placebo training dose, as well as at all other visits, was to be recorded as an AE.

Therefore, no specific laboratory exam or ECG result tabulations will be performed.

5. PLANNED ANALYSES

5.1. FINAL ANALYSIS

Final analyses will be performed for this study. All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sunovion Authorization of this Statistical Analysis Plan, Database lock, Sunovion Authorization of Analysis Sets and Unblinding of Treatment.

5.2. DATA MONITORING COMMITTEE (DMC) ANALYSIS

There will be no DMC analysis for this study.

5.3. INTERIM ANALYSIS

There will be no interim analysis for this study.

6. ANALYSIS POPULATIONS

Agreement and authorization of subjects included/ excluded from each analysis set will be conducted prior to the unblinding of the study.

6.1. ALL SUBJECTS SCREENED [SCR]

The subjects Screened (SCR) will contain subjects who signed the study specific informed consent and completed at least one study related procedure.

6.2. ALL SUBJECTS ENROLLED [ENR]

The all subjects enrolled (ENR) population will contain all subjects who were successfully screened and enrolled into the pre-randomization period of the study.

6.3. ALL SUBJECTS RANDOMIZED [RND]

The all subjects randomized (RND) population will contain all subjects who were randomized into a treatment sequence of the study and were assigned a randomization number.

For analyses and displays based on RND, subjects will be classified according to randomized treatment.

6.4. EFFICACY (EFF) POPULATION

The efficacy (EFF) population will consist of subjects who were randomized, received at least one dose of study treatment, and have a baseline and at least one post-baseline RV measurement within the same period. Should a subject require rescue medication during the approximately 6 hours of efficacy endpoint collection, any efficacy values occurring after the use of the rescue medication will be set to missing. In general, subjects will be analyzed according to randomized treatment.

6.5. SAFETY [SAF] POPULATION

The safety population (SAF) will consist of all subjects who were randomized and received at least one dose of study medication. Subjects will be analyzed according to treatment received.

7. GENERAL CONSIDERATIONS

7.1. REFERENCE START DATE 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 during the randomized treatment period, (Day 1 is the day of the first dose of study medication during randomized treatment period), 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 date then:

  Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

  Study Day = (date of event – reference date).

  In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

7.2. BASELINE

Study baseline is defined as the last non-missing measurement take prior to dosing of randomized study medication on Day 1.

Unless otherwise specified, period baseline will be used for the analysis of change from baseline and will be defined as follows.

- Period 1 Baseline: Predose measurement value collected 45 minutes prior to the dosing during on Day 1. If the predose value on Day 1 has a missing value, then the last non-missing predose measurement (including unscheduled) will be used as the baseline value.
- Period 2 Baseline: Predose measurement value collected 45 minutes prior to the dosing during on Day 9. If the predose value on Day 9 has a missing value, then the last non-missing predose measurement after washout (including unscheduled) will be used as the baseline value.

7.3. UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries.

Listings will include scheduled, unscheduled, early discontinuation data.

7.4. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

7.5. STATISTICAL TESTS

In general, descriptive summaries will be provided where appropriate for each of the endpoints. Continuous outcomes will be summarized for the number of subjects, mean, 95% Confidence Interval (CI) for the mean, SD, median, quartile 1 (Q1), quartile 3 (Q3),

minimum, and maximum. For categorical outcomes, the number and percentage of subjects will be presented.

All statistical inference analyses will be performed with 2-sided tests at a significance level of 0.05, unless otherwise specified. No adjustments for multiplicity will be applied.

7.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated for each period as:

- Test Value at Visit X – Baseline Value

Body mass index (BMI) will be calculated for study baseline as following:

- BMI (kg/m^2) = weight (kg)/height $(m)^2$

7.7. SOFTWARE VERSION

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

8. STATISTICAL CONSIDERATIONS

8.1. 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.

- Period baseline
- Treatment, (GIS, PIS)
- Period, (1,2)
- Sequence, (AB, BA)

8.2. MISSING DATA

Missing safety data will not be imputed.

For the primary analysis of the primary efficacy endpoint, missing observations will be treated as missing at random (MAR). However, sensitivity analyses will be conducted if there is significant amount of missing data (more than 25% subjects have missing primary data after considering rescue medication [i.e. change from baseline of RV at 6 hours postdose]), including missing not at random (MNAR) assumptions.

8.3. MULTIPLE COMPARISONS/ MULTIPLICITY

No multiple comparison procedures will be employed in this study.

8.4. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for this study.

9. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates 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.

10. DISPOSITION AND WITHDRAWALS

The number and percentage of subjects screened (Defined as in Section 5.1), screen failed, enrolled, randomized, dosed, in SAF, EFF, complete each period, having a baseline and at least one post-dose RV measurement before rescue, and complete the study, terminate early will be summarized for all screened subjects, along with reasons of termination, by treatment sequence and treatment group and overall.

Disposition data including dates of completion or early discontinuation and the reason for early discontinuation will be provided in a listing. A listing of screen failure subjects will be provided.

Listings of subjects who failed inclusion/exclusion criteria and subject who fails the continuation criteria will be provided.

11. IMPORTANT PROTOCOL DEVIATIONS

Important protocol deviations (IPDs) will be identified and documented based on a review of potentially IPDs. The potentially IPDs will be identified through programmatic checks of study data, as well as through review of selected data listings. The potentially IPDs to be reviewed include, but are not limited to, subjects who:

- Did not meet inclusion/exclusion criteria.
- Received any disallowed concomitant medication, including rescue medication use during the efficacy endpoint collection.

Possible exclusion of subjects based on IPDs from the EFF population will be decided by Sunovion before the database lock. It should be noted that the identification of any IPDs related to receiving wrong treatment requires unblinded data.

Further details on the identification of IPDs are provided in IPD/BDR listings specification document.

IPDs will be identified for all randomized subjects and presented in data listings.

12. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for overall (unless otherwise specified) based on the EFF and SAF populations.

The following demographic characteristics will be summarized for this study:

- Age (years) - calculated relative to date of consent
- Age group (<65 years, >=65 years)
- Gender
- Race
    - American Indian or Alaska Native
    - Asian
    - Black or African American
    - Native Hawaiian or Other Pacific Islander
    - White
    - Multiracial as is (where more than one race is selected, ie, White/Asian, Black/Other)

- Other
- Other including multiracials
- Non-white (Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islanders, and Other including multiracials)

- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

Each unique multiracial subcategory needs to be presented as collected, i.e. “Asian, American Indian or Alaska Native”. Other than subjects who are White only, all other subjects are considered as non-White.

Following Baseline COPD characteristics will be summarized as well:

- History of Tobacco Use (current, former)
- Number of Pack Years (Number of pack years is calculated as (number of cigarettes per day / 20) x number of years smoked)
- COPD exacerbations within 12 months prior to the screening
- mMRC Dyspnea Scale Grades (0, 1, 2, 3, 4)
- SGRQ component and total score (Symptoms Component, Activity Component, Impacts Component, total score)

The following efficacy endpoints at screening will also be summarized by overall for the EFF and SAF populations:

- Plethysmography (RV, RV% of Predicted Normal, Expiratory Reserve Volume ERV, IC, FRC, TLC, sRaw, Raw for Prebronchodilator at Screening; RV, RV% of Predicted Normal, ERV, IC, FRC, TLC, sRaw, Raw for Postbronchodilator at Screening). See following table for details.

Table 2: Scheduled Measurements of Plethysmography at Screening

	Screening	
Parameter of interest	**Prebronchodilator**	**Postbronchodilator**
RV	X	X
RV% of Predicted normal	X	X

ERV	X	X
IC	X	X
FRC	X	X
TLC	X	X
sRaw	X	X
Raw	X	X

- Spirometry (FEV1, FVC, FEV1/FVC Ratio, FEV1% of Predicted normal; FEV1, FVC, FEV1/FVC Ratio, FEV1% of Predicted normal, post FEV1 improvement, post FEV1 improvement change for Postbronchodilator at Screening). See following table for details.

Table 3: Scheduled Measurements of Spirometry at Screening

	Screening	
Parameter of interest	**Prebronchodilator**	**Postbronchodilator**
FEV1	X	X
FVC	X	X
FEV1/FVC Ratio	X	X
FEV1% of Predicted normal	X	X
Post FEV1 improvement		X
Post FEV1 improvement change		X

Listings of demographic characteristics, baseline COPD characteristics, plethysmography and spirometry endpoints at screening will be provided.

12.1. DERIVATIONS

- St. George's Respiratory Questionnaire (SGRQ) total score

The SGRQ is a questionnaire designed to measure health impairment in patients with asthma and COPD. Each subject will complete the SGRQ on the SGRQ form in eCRF at the clinical site during the screening visit. The SGRQ is a standardized disease specific, 50 item questionnaire designed to measure impact on overall health, daily life, and perceived well being in patients with obstructive airway disease over the past 3 months.

Three component scores are derived from the questionnaire responses:

- Symptoms component
- Activity component
- Impacts component

A single total score is also calculated.

Calculations for each SGRQ component score and SGRQ total score and the approach to handling missing items are provided in Appendix 3.

Summary of absolute values of SGRQ components and total score at Screening will be presented descriptively for overall for the EFF and the SAF Population. If more than one SGRQ assessment occurs on a particular date for the same subject then only the first assessment on that date will be presented.

13. MEDICAL HISTORY

Medical History information will be presented for the SAF and EFF populations.

Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.1 or higher. The number and percentage of subjects in each System Organ Class (SOC) and each Preferred Term (PT) will be summarized for overall. Medical history will be sorted alphabetically by SOC and then by decreasing frequency based on the overall column.

Medical history will be listed.

14. MEDICATIONS

Medications will be presented for the SAF and EFF populations and coded using the WHO Drug Dictionary Global 01SEP2019 Version. All medications will be coded to indication-specific Anatomical Therapeutic Chemical (ATC) classification and PT according to the WHO-DD.

In the case where it is not possible to define a medication as prior, concomitant, the medication will be classified by the worst case; i.e. concomitant.

'Prior' medications are medications which started and stopped prior to date/time of the first study medication during the randomized treatment period.

Concomitant medications during the randomized treatment period will be summarized in tables. These medications will be assigned to different treatments depending on the timing and duration of the medication. Based on the start and stop dates of the concomitant medication, it will be assigned to each treatment given in a treatment period that the medication's use overlaps with. For patients who only complete the first period,

the interval in Treatment Period 1 will be defined as the days on or after first dose in Period 1. Among patients who complete both periods, the intervals in each treatment period will be defined as:

- Treatment Period 1: first dose in Period 1 to day before first dose in Period 2 inclusive.
- Treatment Period 2: on or after first dose in Period 2.

Prior medications will only be presented in listings. All medications that ended before the start date/time of the 1st randomized treatment will be considered as prior medications and will only be presented in listings. Medications that ended before screening will be considered as pre-training medications and will only be presented in the listings as well.

If medication start date is missing, then it will be considered as associated with all treatments received on or prior to the known medication end date. If both start/end dates are missing, the medication will be considered as associated to all treatments received, including the training dose. For medications with partial dates, please see details of imputation rules in Appendix 2.

The number and percentage of subjects using concomitant medication during the randomization treatment period will be summarized for each treatment and overall by ATC level 2 class and PT. Subjects with multiple uses of a medication will be counted only once for a given drug class or PT. If ATC level 2 is missing, ATC level 1 will be used in the table. Concomitant medications will be sorted alphabetically by ATC2 and then by decreasing frequency of PT in the GIS treatment group.

A listing of prior and concomitant medications taken by subjects will be provided.

A listing of rescue medication taken by subjects will be provided.

15. STUDY MEDICATION EXPOSURE

A data listing, by subject, containing the duration of each nebulization will be provided. Since dosing of subjects occurs in the clinic, treatment compliance will not be summarized. The duration of each nebulization is calculated by using the end of nebulization time minus start of nebulization time.

16. STUDY MEDICATION COMPLIANCE

No compliance to study medication will be summarized since study drug administration is done in clinic.

17. EFFICACY OUTCOMES

All efficacy endpoints will be summarized for the EFF population using descriptive statistics. Continuous variables will be summarized using the number of subjects, mean, standard deviation, 95% Confidence Interval, median, Q1 and Q3, minimum, and maximum. Categorical variables will be summarized using counts and percentages. Significance tests will be 2-sided and conducted at an alpha level of 0.05, unless otherwise specified.

17.1. PRIMARY EFFICACY

17.1.1. PRIMARY EFFICACY VARIABLE(S) & DERIVATION(S)

The primary efficacy estimand is defined as the difference between a single dose of GIS and PIS in the mean change of RV from baseline at 6 hours postdose in COPD patients as characterized by the study inclusion/exclusion criteria, in the hypothetical setting where the subjects were able to stay on study and receive their study drug during their treatment periods. Should a subject require rescue medication during the approximately 6 hours of efficacy endpoint collection, then any efficacy values that occur after the use of the rescue medication will be set to missing.

Baseline and postbaseline RV are collected on Plethysmography Study Measurements form of eCRF. The change from baseline in RV at 6 hours postdose will be calculated for each treatment period as RV at 6 hours postdose on the day of treatment minus the period baseline of each treatment period.

Period baseline is defined as the predose RV value collected 45 minutes prior to the dosing during each treatment period (Day 1 for Period 1 and Day 9 for Period 2).

- Period 1 Baseline: Predose RV value collected 45 minutes prior to the dosing during on Day 1. If the predose value on Day 1 has a missing value, then the last non-missing predose measurement (including unscheduled) will be used as the baseline value.
- Period 2 Baseline: Predose RV value collected 45 minutes prior to the dosing during on Day 9. If the predose value on Day 9 has a missing value, then the last non-missing predose measurement after washout (including unscheduled) will be used as the baseline value.

17.1.2. Missing Data Methods for Primary Efficacy Variable(s)

For the primary analysis of the primary efficacy endpoint, missing observations will be treated as missing at random (MAR). If more than 25% subjects have missing primary data (i.e. change from baseline of RV at 6 hours postdose), then placebo-based multiple imputation method will be used for imputation.

17.1.3. Primary Analysis of Primary Efficacy Variable(s)

The primary objective of this study is to compare the efficacy of GIS versus PIS on lung hyperinflation following a single dose, as measured by residual volume (RV) at 6 hours postdose.

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

For the primary analysis of the primary efficacy endpoint, data will be analyzed using a 2-way crossover analysis of covariance (ANCOVA) using the EFF population. The ANCOVA model will include terms for treatment, period and sequence as fixed effects, period baseline as a covariate, and subjects nested within sequence as a random effect. The Kenward and Roger correction for the degrees of freedom will be used. The main estimator of the primary estimand is the Least Squares (LS) mean difference in the change from baseline in RV at 6 hours postdose from the primary ANCOVA model. LS mean (and 95% CI) for each treatment group and LS mean (and 2-sided 95% CI), and the associated p-value for the difference between the single dose of GIS and PIS will be displayed. If this model fails to converge, a paired t-test will be used to evaluate the treatment difference. The mean (and 95% CI) for each treatment group and the mean (and 2-sided 95% CI), and the associated p-value for the difference between the single dose of GIS and PIS will be displayed. Statistical appendix outputs for normality checks will be provided, i.e. qqplot and Shapiro-Wilk statistics.

The SAS code anticipated to be used for analysis of this primary efficacy endpoint is as follows:

```
PROC MIXED DATA=dataset;
        BY postdose_time_point;
        CLASS treatment sequence subject period;
MODEL CFB= Baseline treatment period sequence/DDFM=KENWARDROGER RESIDUAL OUTP=outresidual;
        RANDOM INT / SUBJECT=subject(sequence);
        LSMEANS treatment / PDIFF CL E;
RUN;
```

Actual and change from baseline values for the primary endpoint will also be summarized using descriptive statistics by treatment sequence.

Graphical displays of the LS Mean (95% CI) and the LS Mean Difference (95% CI) from the above Change from baseline model for GIS versus PIS for RV will be presented together with ANCOVA results of RV at other postdose time point (1, 2, 3, 4) using the EFF population.

Subject profile plots for the RV efficacy endpoint at baseline and each post-baseline time point will be presented by subject, period and treatment sequence using the EFF population. Group means of RV change from baseline across time by period will also be plotted for each treatment sequence using the EFF population.

17.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE

If more than 25% subjects have missing primary data after considering rescue medication (i.e. change from baseline of RV at 6 hours postdose), to address early dropouts under the assumption of missing not at random (MNAR), a pattern-mixture model (PMM) using a placebo-based multiple imputation method (O'Kelly 2014; Ratitch 2011) will be performed as sensitivity analyses to explore the robustness of the primary ANCOVA results for the primary analysis based on the Efficacy population.

All subjects randomized are included in pattern-mixture model with placebo-based multiple imputation.

The ANCOVA model used in the primary analysis makes the assumption that data are MAR. However, the missing data mechanism may or may not be at random. Sensitivity to the missing data assumption will be tested by using the PMM with placebo-based multiple imputation method, exploring the robustness of the ANCOVA results of the primary efficacy analysis. In this analysis, missing values in the GIS (25 mcg/day) treatment group will be imputed based on data of the placebo group, assuming that after withdrawal or considering rescue medication, subjects from the GIS (25 mcg/day) group will exhibit the same future evolution of change from baseline of RV as subjects from the placebo group, and that subjects who discontinue from the placebo group will exhibit the same future evolution of change from baseline of RV as subjects in the placebo group remaining in the study. This approach does not assume a sustained benefit of experimental treatment after discontinuation.

Two separate imputation procedures are used to impute missing values. Firstly, the Markov chain Monte Carlo (MCMC) method is used to perform partial imputation to obtain datasets with monotone missing patterns. Then a sequential regression multiple imputation method is used to impute the monotone missing values.

Under the assumption that the RV have a multivariate normal distribution, the MCMC method is used to impute only intermittent missing values (using the SAS MI procedure

with MCMC statement), by using a data augmentation algorithm, with each iteration n consisting of an imputation step and a posterior step. The imputation step uses a random draw of θ(n), parameter of the joint imputation model, to sample missing values from a conditional distribution P(Ymis|x, yobs, θ(n)), obtaining ymis(n), the subset of missing values that need to be filled in to achieve monotone missingness. The posterior step simulates a new draw of the parameter θ(n+1) from the posterior distribution given the current monotone missing data P(θ|x, yobs, ymis(n)) with a non-informative Jeffreys prior. Treatment group will be taken into account for this imputation (ie, missing data at intermediate time points will be imputed for each treatment group using no-missing data from all subjects within the treatment group). These steps are repeated to obtain 1000 datasets with monotone missingness. The random seed number is 12345.

The remaining monotone missing data will be imputed using sequential regression multiple imputation, where a separate regression model is estimated for imputation of each variable (ie, RV measurement at each time point). Imputation of values in the placebo group will assume MAR. Imputation of values in the GIS (25 mcg/day) group will be done as if the subject had been a member of the placebo group. Missing values in the GIS (25 mcg/day) group will be imputed using the imputation model of the placebo group, ie, conditional on subject values observed at time points prior to discontinuation. Each sequential regression model (ie, for imputation of values at a given time point) will include explanatory variables for all previous (Baseline, 1hour post baseline, 2 hour post baseline, 3 hour post baseline, 4 hour post baseline, 6 hour post baseline) values of RV measurement. Missing values at a given time point in placebo and GIS (25 mcg/day) treatment groups will be imputed from the same imputation model, conditional on subject values observed or imputed at previous time points. The SAS MI procedure with the MONOTONE REG statement is used to specify that the regression method will be used for the imputation, and the MNAR statement with MODEL option will be used for the RV measurement at each postbaseline visit to specify that only observations from the placebo group should be used to estimate the imputation model. The random seed number is 56789.

No rounding restriction will be applied to imputed RV measurement. The imputed RV measurements must be within the range of 0 to 13.

Each of the 1000 imputed datasets will be analyzed using the same ANCOVA model as the primary efficacy analysis at 6 hours post-dose. Results from the analysis of each imputed dataset, ie, the LS means of each treatment group, the LS mean treatment difference, and their standard errors, will be combined using Rubin's imputation rules (using the SAS MIANALYZE procedure) to produce pooled LS mean estimates, their standard errors and 95% CI, and a pooled p-value for the test of null hypothesis of no treatment effect.

17.1.5. SUBGROUP ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

No subgroup analysis for this study.

17.1.6. SUPPORTIVE ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

Additional supportive analysis will be conducted for change from baseline in RV at each postdose time point. The difference in change from baseline between GIS and PIS treatment groups will be analyzed using the Wilcoxon rank-sum test. 95% CI for the median will be provided using the Hodges-Lehmann method. The Wilcoxon rank-sum test will be performed on the within-subject change from baseline difference between the two periods. The null hypothesis is that the distribution of the differences (GIS – PIS) in sequence AB is equal to the distribution of the differences (PIS - GIS) in sequence BA, which is equivalent to examining the treatment effect of GIS minus Placebo.

The SAS code anticipated to be used for analysis of this supportive analysis is as follows:

```
PROC NPAR1WAY DATA=dataset WILCOXON HL ALPHA=0.05;
        BY time_point;
        CLASS sequence;
        VAR period_diffinchange;
        EXACT WILCOXON/ALPHA=0.05;
RUN;
```

17.2. OTHER EFFICACY

All other efficacy endpoints will be analyzed using the EFF population.

All other efficacy endpoints will be analyzed using the ANCOVA model similar to the primary efficacy endpoint with appropriate baseline as a covariate.

17.2.1. OTHER EFFICACY VARIABLES & DERIVATIONS

17.2.1.1. Other Efficacy Variables - Change from baseline

Changes from baseline in EVR, IC, FRC, TLC, sRaw, Raw and FEV1, FVC at 6 hrs postdose will be calculated similar to the primary analysis endpoint. All other postdose lung volume endpoints (RV, IC, FRC, TLC, sRaw and Raw) at 1, 2, 3 and 4 hours postdose will be derived similar to the primary endpoint.

17.2.1.2. Other Efficacy Variables - Standardized change from baseline

The following plethysmography endpoints at specific postdose timepoints will be calculated:

- RV (RV AUC0-3h , RV AUC0-4h, RV AUC0-6h);
- ERV (ERV AUC0-3h , ERV AUC0-4h, ERV AUC0-6h);
- IC (IC AUC0-3h, IC AUC0-4h, IC AUC0-6h);
- FRC (FRC AUC0-3h, FRC AUC0-4h, FRC AUC0-6h);
- TLC (TLC AUC0-3h , TLC AUC0-4h, TLC AUC0-6h);
- sRAW (sRAW AUC0-3h, sRAW AUC0-4h, sRAW AUC0-6h);
- RAW (RAW AUC0-3h, RAW AUC0-4h, RAW AUC0-6h).

The standardized change from baseline values will be calculated in each period.

The standardized area under the change from baseline curve, i.e. AUC0-6h, will be calculated using the trapezoidal rule. If a subject has missing measurements intermittently, then those missing values will be ignored, and the trapezoidal rule will simply span the missing time point(s).

The general AUC formula by the trapezoid rule is given below:

$$AUC_{(t_0-t_n)} = \sum_{i=1}^{n} \frac{c_i + c_{i-1}}{2}(t_i - t_{i-1})$$

Where:

t_0 = the time of the baseline measurement

c_0 = 0 (change from baseline measurement at baseline is always 0)

c_i = the change from baseline measurement at time t_i

t_n = the time of the last measurement

n + 1 = the number of non-missing time points

Actual times will be used in all calculations, using the start time of dosing as the reference time (i.e. time 0). For example, the Hour 6 time point will be used for change from baseline AUC0-6h. If the Hour 6 time point is missing, then the change from baseline measurement AUC0-6h calculation will be based on the time interval up to the last non-missing time point prior to Hour 6.

If a subject has a missing baseline value, then that subject will have missing AUC values.

The standardized area under the curve is defined as:

$$\frac{AUC_{(t_0-t_n)}}{(t_n-t_0)}$$

Where (t_n-t_0) is the total actual time (in minutes) used for calculation of the $AUC_{(t0\text{-}tn)}$.

17.2.2. Missing Data Methods for Other Efficacy Variable(s)

Missing observations will be treated as missing at random (MAR) and no data imputation will be performed.

17.2.3. Analysis of Other Efficacy Variables

17.2.3.1. Analysis of Other Efficacy Variables - Change from baseline

Changes from baseline in ERV, IC, FRC, TLC, sRaw, Raw and FEV1, FVC at 6 hrs postdose will be analyzed similar to the primary analysis endpoint. All other postdose lung volume endpoints (RV, ERV, IC, FRC, TLC, sRaw and Raw) at 1, 2, 3 and 4 hours postdose will also be analyzed similar to the primary endpoint.

Mean change from baseline in RV at each postdose time point will be plotted by treatment using the EFF population.

17.2.3.2. Analysis of Other Efficacy Variables - Standardized change from baseline

These standardized change from baseline variables for plethysmography endpoints will be analyzed similar to the primary analysis in Section 16.1.

Subject profile plots for standardized change from baseline in RV AUC0-3h, AUC0-4h , and AUC0-6h will be presented by subject, period and treatment sequence using the EFF population. Group means of standardized change from baseline in RV AUC0-3h, AUC0-4h, and AUC0-6h by period will also be plotted for each treatment sequence using the EFF population.

17.2.4. Sensitivity Analysis of Other Efficacy Variables

No sensitivity analysis for the other efficacy variables will be performed.

17.2.5. Subgroup Analysis of Other Efficacy Variable(s)

No subgroup analysis for other efficacy variables will be performed.

17.2.6. SUPPORTIVE ANALYSIS OF OTHER EFFICACY VARIABLE(S)

17.2.6.1. Supportive analysis of Other Efficacy Variables- Change from baseline

The difference between GIS and PIS treatment groups for change from baseline in RV at 1,2,3,4 hrs postdose and ERV, IC, FRC, TLC, sRaw, Raw at 1,2,3,4, 6 hrs postdose and FEV1, FVC at 6 hrs postdose will be analyzed using the Wilcoxon rank-sum test similar to the supportive analysis for the primary endpoint in Section 16.1.5.

17.2.6.2. Supportive analysis of Other Efficacy Variables - Standardized change from baseline

Following endpoints will be analyzed using the Wilcoxon rank-sum test similar to the supportive analysis for primary endpoint in Section 16.1.5.

- RV (RV AUC0-3h, RV AUC0-4h, RV AUC0-6h);
- ERV (ERV AUC0-3h, ERV AUC0-4h, ERV AUC0-6h);
- IC (IC AUC0-3h, IC AUC0-4h, IC AUC0-6h);
- FRC (FRC AUC0-3h, FRC AUC0-4h, FRC AUC0-6h);
- TLC (TLC AUC0-3h, TLC AUC0-4h, TLC AUC0-6h);
- sRAW (sRAW AUC0-3h, sRAW AUC0-4h, sRAW AUC0-6h);
- RAW (RAW AUC0-3h, RAW AUC0-4h, RAW AUC0-6h).

17.3. EXPLORATORY ENDPOINTS

17.3.1. DATA COLLECTED USING THE ACCELERATEIQ SYSTEM

A listing of Date/Time of VitalPatch Biosensor application information collected on eCRF will be provided. A separate SAP will be created for the AccelerateIQ System data by AccelerateIQ.

17.3.2. CLINIC VISIT VITAL SIGNS

Vital signs will be collected at Screening and 45 (± 15) minutes prior to dosing and 60 (± 15) minutes postdose in each period during the clinic visits. Period baseline is defined as the last non-missing predose value on each treatment day. The following Vital Signs measurements will be reported for this study:

- Supine Systolic Blood Pressure (mmHg)

- Supine Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (^{0}C)

Summary statistics of observed clinic visit vital sign measurements and change from baseline will be presented by treatment group. If period 1 baseline is missing, the screening value will be used as period 1 baseline.

A listing of clinic site vital sign measurements will be presented as well.

17.3.3. CORRELATIONS BETWEEN SELECTED EFFICACY ENDPOINTS

Pearson's Correlations between plethysmography and spirometry endpoints will be presented by treatment group at 6 hours post dose. For example, correlation between change from baseline in RV and change from baseline in FEV1, RV and FVC, ERV and FEV1, ERV and FVC, and so on.

18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.

There will be no statistical comparisons between the treatment groups for safety data.

18.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 22.1 or higher.

Adverse events (AEs) are untoward medical occurrences associated with the use of a drug in humans, whether or not considered drug related.

AEs during the randomized treatment period will be defined as AEs:

- That occurred on or after the first dose of study medication,
- With a missing start date and a stop date on or after the first dose of study medication
- with both a missing start and stop date.

For subject incidence summaries, each subject will be counted only once within each SOC and within each preferred term in the treatment group.

For the Crossover Phase, the AE will be assigned to the period that corresponds to the latest treatment received prior to the onset. For example, if the start date of AE is on or after date/time of the treatment in period 1 and before treatment in period 2, the AE will be assigned to treatment in period 1; if the start date of AE is after training dose at screening and before 1st dose in period 1, it will be assigned to the training dose; if the start date of AE is before training dose at screening, it will be considered as pretreatment dose AE. An AE that starts on or after the date/time of the last treatment will be assigned to the treatment group associated with the last treatment.If the AE start date is missing, then the AE will be assigned to all treatments received.

An overall summary of number of subjects within each of the categories described in the sub-section below, will be provided as specified in the shells.

AEs during the randomized treatment period mentioned in the following sub-section will be summarized and presented by treatment group and by MedDRA SOC and PT. AEs will be sorted alphabetically by SOC and then by decreasing frequency of PT of the GIS treatment group.

A listing of all AEs, SAEs, AEs leading to discontinuation will be presented.

Listings will include both AEs during the randomized treatment period and AEs related to training dose and pre-training dose AEs. A listing of AEs for screen failures will be presented as well.

18.1.1. ALL AEs DURING THE RANDOMIZED TREATMENT PERIOD

Number of events and subject Incidence of all AEs will be presented by SOC and PT by treatment group. Subject incidence of all AEs will also be presented by SOC and PT breaking down further by maximum severity and relationship to study medication by treatment group.

18.1.1.1. Severity During the Randomized Treatment Period

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

18.1.1.2. Relationship to Study Medication During the Randomized Treatment Period

Relationship, as indicated by the Investigator, is classed as “not related”, “possibly related”, “probably related”, “definitely related” (increasing severity of relationship). A “related” AE is defined as an AE with a relationship to study medication as ”possibly related” or ”probably related” or “definitely related” to study medication. AEs with a

missing relationship to study medication will be regarded as "definitely related" to study medication. If a subject reports the same AE more than once within that treatment, SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries. For example, if a subject reports more than one AE within the same treatment, SOC and PT, and any are related, it will be summarized as related.

18.1.2. AEs Leading to Study Discontinuation during the randomized treatment period

AEs leading to permanent discontinuation of study medication will be identified by using the "Caused Study Discontinuation" checked as "Yes" on adverse event page on eCRF. These should match the AE action taken="Drug Withdrawn" on the AE CRF page.

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

18.1.3. Serious Adverse Events during the randomized treatment period

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious AEs by SOC and PT by treatment group will be prepared.

18.1.4. Non-serious Adverse Events With a 5% Cutoff during the randomized treatment period

Non-serious AEs events with a 5% cutoff is defined as non-serious AEs that occur for more than 5% patients within any treatment group. Non-serious AEs events with a 5% cutoff will be presented by SOC and PT by treatment group.

18.2. Deaths

If any subjects die during the study, the information will be presented in a data listing.

18.3. Laboratory Evaluations

Laboratory test results are only kept at site as source data and not collected on CRF. Therefore, no laboratory exam result tabulations will be performed. Only pregnancy test result will be recorded and listed.

18.4. ECG EVALUATIONS

ECG results are only kept at site as source data and not collected on CRF. Therefore, no ECG exam result tabulations will be performed.

18.5. PHYSICAL EXAM EVALUATIONS

Findings from the physical examination will be presented as follows: pre-existing clinically significant conditions recorded as medical history will be summarized, and new clinically significant conditions recorded as an AE. No specific physical exam results outputs will be performed.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

DATES & TIMES

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

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

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

Treatment Group	For Tables, Listings and Graphs
Placebo	Placebo
GIS 25 mcg Single Dose	GIS 25 mcg Single Dose

Randomized Treatment Sequence	For Tables, Listings and Graphs
GIS 25 mcg Single Dose - Placebo	Treatment sequence AB
Placebo - GIS 25 mcg Single Dose	Treatment sequence BA

PRESENTATION OF VISITS

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

Long Name (default)	Short Name
Screening	Scr (V0)
Period 1	P1 (V1)

Long Name (default)	Short Name
Period 2	P2 (V2)
Follow-up/Early Termination	FU/ET

LISTINGS

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

- subject ID,
- randomized treatment sequence, date (where applicable),
- For listings where non-randomized subjects are included, these will appear at the end of the listing.

APPENDIX 2. PARTIAL DATE CONVENTIONS FOR CONCOMITANT MEDICATIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	Follow algorithm in Section 14.
	Partial	Impute stop date as latest possible date (i.e. the earlier one of the following two: last day of month if day unknown or 31st December if day and month are unknown, date of the last visit), then follow algorithm in Section 14.
	Missing	Considered as asscociated with all treatments received on or after the known medication start date.
Partial	Known	Impute start date as earlist possible date (i.e. 1st day of month if day unknown or 1st Jan if day and month are unknown), then follow algorithm in Section 14.
	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. the earlier one of the following two: last day of month if day unknown or 31st December if day and month are unknown, date of the last visit), then follow algorithm in Section 14.
	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 consider the medication as asscociated with all treatments received on or after the imputed medication start date.
Missing	Known	Considered as asscociated with all treatments received on or prior to the known medication end date.
	Partial	Impute stop date as latest possible date (i.e. the earlier one of the following two: last day of month if day unknown or 31st December if day and month are unknown, date of the last visit), then consider the medication as asscociated with all treatments received on or prior to the imputed medication stop date.
	Missing	The medication will be considered as associated to all treatments received, including the training dose.

APPENDIX 3. SGRQ QUESTIONNAIRE AND SCORING ALGORITHMS

Q1. Over the past 3 months, I have coughed:

a. Almost every day	80.6
b. Several days a week	63.2
c. A few days a month	29.3
d. Only with respiratory infections	28.1
e. Not at all	0.0

Q2. Over the past 3 months, I have brought up phlegm (sputum):

a. Almost every day	76.8
b. several days a week	60.0
c. A few days a month	34.0
d. Only with respiratory infections	30.2
e. Not at all	0.0

Q3. Over the past 3 months, I have had shortness of breath:

a. Almost every day	87.2
b. Several days a week	71.4
c. A few days a month	43.7
d. Only with respiratory infections	35.7
e. not at all	0.0

Q4. Over the past 3 months, I have had wheezing attacks:

a. Almost every day	86.2
b. Several days a week	71.0
c. A few days a month	45.6
d. Only with respiratory infections	36.4
e. Not at all	0.0

Q5. How many times during the past 3 months have you suffered from severe or very unpleasant respiratory attacks?

a. More than 3 times	86.7
b. 3 times	73.5
c. 2 times	60.3
d. 1 time	44.2
e. None of the time	0.0

Q6.How long did the worst respiratory attack last?

a. A week or more	89.7
b. 3 or more days	73.5
c. 1 or 2 days	58.8
d. Less than a day	41.9

Q7. Over the past 3 months, in a typical week, how many good days (with few respiratory problems) have you had?

a. No good days	93.3
b. 1 or 2 good days	76.6
c. 3 or 4 good days	61.5
d. Nearly every day was good	15.4
e. Every day was good	0.0

Q8.If you wheeze, is it worse when you get up in the morning?

a. No	0.0
b. Yes	62.0

Q9. How would you describe your respiratory condition?

a. The most important problem I have	83.2
b. Causes me quite a lot of problems	82.5
c. Causes me a few problems	34.6
d. Causes no problem	0.0

Q10. If you ever held a job:

a. My respiratory problems made me stop working altogether	88.9
b. My respiratory problems interfere with my job or made me change my job	77.6
c. My respiratory problems do not affect my job	0.0

Q11. These are questions about what activities usually make you feel short of breath these days.

a. Sitting or lying still	90.6
b. Washing or dressing yourself	82.8
c. Walking around the house	80.2
d. Walking outside on level ground	81.4
e. Walking up a flight of stairs	76.1
f. Walking up hills	75.1
g. Playing sports or physical activities	72.1

Q12. These are more questions about your cough and shortness of breath these days.

a. Coughing hurts	81.1
b. Coughing makes me tired	79.1
c. I am short of breath when I talk	84.5
d. I am short of breath when I bend over	76.8
e. My coughing or breathing disturbs my sleep	87.9
f. I get exhausted easily	84.0

Q13. These are questions about other effects that your respiratory problems may have on you these days.

a. My cough or breathing is embarrassing in public	74.1
b. My respiratory problems are a nuisance to my family, friends or neighbors	79.1
c. I get afraid or panic when I cannot catch my breath	87.7
d. I feel that I am not in control of my respiratory problem	90.1
e. I do not expect my respiratory problems to get any better	82.3
f. I have become frail or an invalid because of my respiratory problems	89.9
g. Exercise is not safe for me	75.7
h. Everything seems too much of an effort	84.5

Q14. These are questions about your respiratory treatment.

a. My treatment does not help me very much	88.2
b. I get embarrassed using my medication in public	53.9
c. I have unpleasant side effects from my medication	81.1
d. My treatment interferes with my life a lot	70.3

Q15. These are questions about how your activities might be affected by your respiratory problems.

a. I take a long time to get washed or dressed	74.2
b. I cannot take a bath or shower, or I take a long time to do it	81.0
c. I walk more slower than other people my age, or I stop to rest	71.7
d. Jobs such as household chores take a long time, or I have to stop to rest	70.6
e. If I walk up one flight of stairs, I have to go slowly or stop	71.6
f. If I hurry or walk fast, I have to stop or slow down	72.3
g. My breathing makes it difficult to do things such as walk up hills, carry things upstairs, light gardening such as weeding, dance, bowl or play golf	74.5
h. My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk briskly	71.4
i. 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

Q16. We would like to know how your respiratory problems usually affects your daily life.

a. I cannot play sports or do other physical activities	64.8
b. I cannot go out for entertainment or recreation	79.8
c. I cannot go out of the house to do the shopping	81.0
d. I cannot do household chores	79.1
e. I cannot move far from my bed or chair	94.0

Q17. Now please check the box (one only) that you think best describes how your respiratory problems affect you:

a. It does not stop me doing anything I would like to do	0.0
b. It stops me doing one or two things I would like to do	42.0
c. It stops me doing most of the things I would like to do	84.2
d. It stops me doing everything I would like to do	96.7

Score calculation

Each questionnaire response has a unique empirically derived 'weight' (Appendix 3). The lowest possible weight is zero and the highest is 100.

Each component of the questionnaire is scored separately in three steps.

I. The weights for all items with a positive response are summed.

II. The weights for missed items are deducted from the maximum possible weight for each component and total score.

III. The score is calculated by dividing the summed weights by the adjusted maximum possible weight for that component and expressing the result as a percentage:

$$\text{Score} = \frac{\text{Summed Weights from Positive Items in that Component}}{\text{Sum of Weights for all Items in that Component}} \text{ x } 100$$

The total score is calculated in a similar way

$$\text{Score} = \frac{\text{Summed Weights from Positive Items in the Questionnaire}}{\text{Sum of Weights for all Items in the Questionnaire}} \text{ x } 100$$

The maximum possible weights are the maximum possible weights that could be obtained for the worst possible state of the patients. An increase in score indicates a worsening state of a subject.

The sum of the maximum possible weights for each component and Total are

Symptoms component	662.5
Activity	1209.1
Impacts	2117.8
Total	3989.4

Note: these are the maximum possible weights that could be obtained for the worst possible state of the patient.

The questions in the questionnaire are split into components as follows:

Symptoms Component

This is calculated from the summed weights for the positive responses to questions 1 to 8 of the SGRQ questionnaire.

Activity Component

This is calculated from the summed weights for the positive responses to questions 11 and 15 of the SGRQ questionnaire.

Impacts Component

This is calculated from the summed weights for the positive responses to questions 9-10, 12-14 and 16-17 of the SGRQ questionnaire.

Total Score

The total score is calculated by summing all positive responses in the questionnaire and expressing the result as a percentage of the total weight for the questionnaire.

It will be noted that the questionnaire requests a single response to questions 1-7, 9-10, and 17.

Handling Missing Items

It is better not to miss items and any missing items are the fault of the investigator, not the patient. We have examined the effect of missing items and recommend the following methods:

Symptoms

The Symptoms component will tolerate a maximum of 2 missed items. The weight for the missed item is subtracted from the total possible weight for the Symptoms component (662.5) and from the Total weight (3989.4).

Activity

The Activity component will tolerate a maximum of 4 missed items. The weight for the missed item is subtracted from the total possible weight for the Activity component (1209.1) and from the Total weight (3989.4).

Impacts

The Impacts component will tolerate a maximum of 6 missed items. The weight for the missed item is subtracted from the total possible weight for the Impacts component (2117.8) and from the Total weight (3989.4).

Should Question 10 “If you ever held a job” be skipped because the subject has not worked, it will be assigned a weight of 0. If more than 24% of items are missing, then the total score and each of the component scores should be set to missing.