AstraZeneca

Statistical Analysis Plan

Study Code	PT003018 / FLUI-2015-139
NCT #	NCT02643082

A Randomized, Double-Blind, Two Treatment, Two Period, Chronic Dosing (2 Weeks), Cross-Over, Single-Center Study to Evaluate the Effects of PT003 and Placebo MDI on Specific Image Based Airway Volumes and Resistance in Subjects With Moderate to Severe COPD.

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Edition Number 1
[redacted]

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Study Statistician

[redacted]

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Global Product Statistician [redacted]

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ATC	Anatomic Therapeutic Class
ATS	American Thoracic Society
BID	Bis In Die, twice daily
CFD	Computational Fluid Dynamics
COPD	Chronic Obstructive Pulmonary Disease
CSR	Clinical Study Report
CT	Computed Tomography
ECG	Electrocardiograms
eCRF	electronic Case Report Form
ERS	European Respiratory Society
FEF25-75	Forced Expiratory Flow between 25% to 75% of FVC
FEV_1	Forced Expiratory Volume In 1 Second
FRC	Functional Residual Capacity
FRI	Functional Respiratory Imaging
FVC	Forced Vital Capacity
GFF	Glycopyrronium and Formoterol Fumarate
GOLD	Global initiative for chronic Obstructive Lung Disease
HFA	Hydrofluoroalkane
IC	Inspiratory Capacity
IPD	Important Protocol Deviation
iRaw	Image based Airway Resistance
ITT	Intent-To-Treat
iVaw	Image based Airway Volume
iVlobe	Image based Lobar Volume
LUL	Left Upper Lobe
LL	Lower Lobe
LLL	Left Lower Lobe
MDI	Metered Dose Inhaler
mITT	Modified Intent-To-Treat
PFT	Pulmonary Function Test
Raw	Airway Resistance
RLL	Right Lower Lobe
RML	Right Middle Lobe
RUL	Right Upper Lobe

Abbreviation or special term	Explanation
RV	Residual Volume
sGaw	Specific Airway Conductance
siRaw	Specific Image based Airway Resistance
siVaw	Specific Image based Airway Volume
sRaw	Specific Airway Resistance
TEAE	Treatment Emergent Adverse Event
TLC	Total Lung Capacity
TP	Treatment Period
UA	Upper Airway
UL	Upper Lobe
WHO-DD	World Health Organization Drug Dictionary

AMENDMENT HISTORY

Date	Brief description of change
	N/A

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objectives

- To assess the effect of treatment with Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (GFF MDI), twice daily (BID) compared with Placebo MDI on specific image-based airway volumes and resistance in subjects with moderate to severe chronic obstructive pulmonary disease (COPD) following chronic dosing after approximately two weeks treatment.

1.1.2 Secondary objectives

- To compare the effects of GFF MDI on various Functional Respiratory Imaging (FRI) parameters.

- To compare the effects of GFF MDI and Placebo MDI on pulmonary function test (PFT) parameters.

1.1.3 Safety Objective

To assess the safety of GFF MDI in subjects with moderate to severe COPD based on adverse events (AEs), and any clinically relevant findings from vital sign measurements, electrocardiograms (ECGs), physical examination findings and clinical laboratory evaluations.

1.2 Study design

This is a single center, double-blind, two treatment, two period, full cross-over, chronic dosing (2 weeks) study to assess the effects of GFF MDI (14.4/9.6 µg BID) compared with Placebo MDI BID on specific image-based airway volumes and resistance in subjects with moderate to severe COPD.

Approximately 20 patients will be randomised to one of two sequences (GFF MDI followed by Placebo MDI or Placebo MDI followed by GFF MDI)

The sensitivity of the study increases with the crossover design where each subject acts as his/her own control. In this study the calculation of airway dimension parameters between the active compound and the placebo will be compared within the same subject after the administration of both the active compound as well as the placebo.

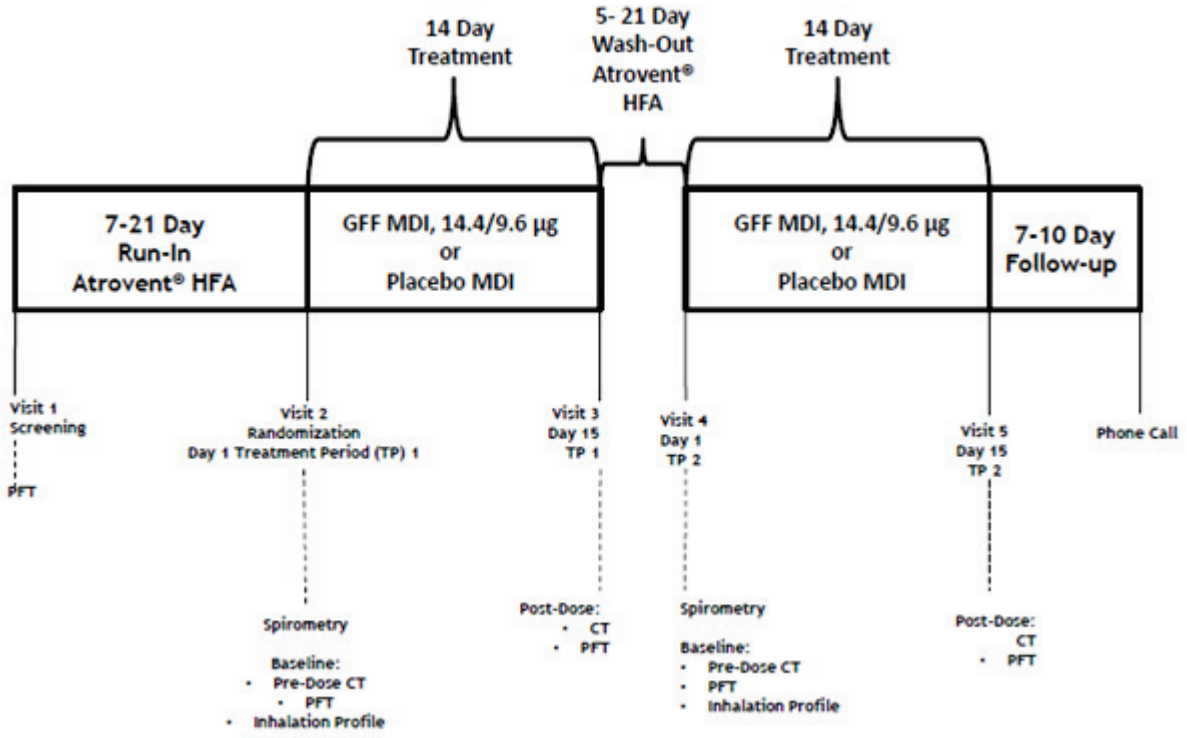
This single-center study will be conducted at one site in Belgium, with the site contributing approximately 20 randomized subjects with moderate to severe COPD.

Study Duration:

Each subject will receive in total study treatment for approximately 4 weeks in two separate treatment periods of two weeks. Between the Treatment Periods there will be a washout

period of 5-21 days. The entire study is scheduled to take approximately 13 weeks for each individual subject.

Study design chart



Computed Tomography (CT)-scans during study:

On Day 1 of each Treatment Period [Visit 2 and Visit 4] a baseline measurement inspiratory scan (total lung capacity [TLC] scan) and expiratory scan (functional residual capacity [FRC] scan) will be conducted. During Visit 2 an additional scan of the upper airway (UA) will be taken. Post dose measurement inspiratory scan (total lung capacity [TLC] scan) will be taken after approximately 2 weeks of treatment with either GFF MDI or Placebo MDI on Day 15 (± 5 days) (Visit 3 and Visit 5). Post dose activities should be started 1 hour after dosing on Visit 3 and Visit 5 and should be concluded within 2.5 hours after dosing.

1.3 Number of subjects

Approximately 20 subjects with moderate to severe COPD will be randomized into the study

[redacted] A sample size calculation (power goal 90%, alpha 0.05) revealed that in order to have a well-powered study with change in imaging based airway volume as primary outcome parameter, a total of 7 subjects would be required (De Backer, 2012). This is based upon powering for a difference of around 1 mL in iVaw and assuming a standard deviation of within subject differences of around 0.6 mL. Similarly, 17 subjects would be required for the image based airway resistance. If the significance level for the volume is set to 0.025 by the Hochberg's step-up procedure, 8 subjects would be required. It can be assumed that a good power will be obtained when including 20 subjects.

2. ANALYSIS SETS

2.1 Definition of analysis sets

The following analysis populations are defined in this study:

2.1.1 Intent-To-Treat (ITT) population

The ITT Population is defined as all subjects who are randomized to treatment. Data are analysed by randomized treatment regardless of the treatment actually received.

2.1.2 Modified Intent-To-Treat (mITT) population

The modified Intent-to-Treat (mITT Population) is a subset of the ITT population including subjects who received treatment and have post treatment efficacy data from both Treatment Periods. Data judged to be impacted by important protocol deviations will be determined prior to unblinding and excluded. Statistical tabulations and analyses will be by randomized treatment, but data obtained after subjects receive an incorrect treatment will be excluded from the affected periods.

2.1.3 Safety population

The Safety Population is defined as all subjects who are randomized to treatment and receive at least one dose of the study treatment. Statistical analyses and tabulations will be by the treatment actually received.

2.1.4 Population for analyses

Analyses will be performed as follows:

Demographics will be summarized for the ITT population. Extent of exposure will be summarized for the Safety Population. The Safety Population will be used to summarize safety data.

Efficacy analyses will be performed for the ITT Population. If the mITT Population differs from the ITT Population it will be used to conduct sensitivity analyses for the co-primary endpoints.

2.2 Violations and deviations

Only Important Protocol Deviations (IPDs) will be listed or tabulated. These are defined as those protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. These will be identified based upon blinded data, before database lock.

The following will be considered important protocol deviations:

- Patient randomized despite not meeting key inclusion criteria, including:
  - Patients not meeting COPD diagnosis (as defined by ATS/ERS) and severity criteria (FEV_1/FVC ratio of <0.70 and post-bronchodilator FEV_1 >30% and <80% of predicted normal) as per inclusion criteria 5 and 7.
  - Patients meeting exclusion criteria for other respiratory disease as per exclusion criteria 4, including diagnoses of asthma.
- Patient received incorrect study drug
- Prohibited concomitant COPD medication taken during the study, defined as the classes of medications listed in table 5-1 of the protocol, received after visit 2, other than those provided by the sponsor.
- Developed discontinuation criteria but not withdrawn from study or discontinued investigational product

Randomization errors

If a subject is given a treatment pack for a different patient or is randomized out of chronological order, he will be included in the statistical analysis. If a subject would receive the same treatment twice, this will be considered an important protocol deviation and sensitivity analyses will be conducted using the mITT population.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Efficacy Endpoints

3.1.1 Definition of baselines

Efficacy baseline assessments are taken pre-dose at Day 1 of each Treatment Period (TP) (Visits 2 and 4). The mean of the available pre-dose assessments across both of these visits will be taken as the subject-average baseline. The mean of the available pre-dose assessments at each of Visit 2 and Visit 4 respectively will be taken as the period-dependent baseline for that respective TP.

For spirometry and plethysmography endpoints the subject-average baseline will be used. That is the mean of all available pre-dose values conducted at Day 1 of each TP will be used to establish baseline. For spirometry the mean of the pre-dose -60 and -30 minute values at Visit 2 and Visit 4 will be averaged. In patients missing either of these assessments the single value from that visit will be used. Baselines for plethysmography endpoints will be based upon the -30 minute assessments.

For FRI parameters subject-average baselines will be derived for each patient as the mean of the baselines across all lobes and periods. Similarly subject-by-period average baselines will be derived across lobes at the subject by period level. These will be used as covariates in sensitivity analyses, but the primary analysis will be conducted on absolute values at Day 15 without using baseline covariates.

3.1.2 Treatment periods and visit windows

There will be two treatment periods in this study. The first day on which a study treatment is received is Treatment Day 1 (for that study treatment and period). Treatment day is numbered sequentially thereafter until washout is begun or a subsequent study treatment is received. Each treatment period is intended to last until Day15.

No study time windows will be derived for the reporting of data. Data will be reported according to the protocol-scheduled day. Efficacy data obtained during unscheduled visits after Day 1 will be allocated to Day 15 within the same treatment period if the Day 15 visit is missing. For analysis of spirometry data by time point, if multiple values are collected the last available assessment will be used for a given nominal time point.

3.1.3 Primary Efficacy Endpoints

FRI Parameters:

The co-primary endpoints of this study are as follows:

- Specific Image based airway volume (siVaw): Absolute value in Airway Volume (iVaw) relative to the lobar volume at Day 15.

- Specific Image based airway resistance (siRaw): Absolute value in Airway Resistance relative to the lobar volume at Day 15.

For FRI parameters data is generated within each of the five lobes of the lung (right upper lobe, right middle lobe, right lower lobe, left upper lobe and left lower lobe). Only the trimmed iVaw values will be taken for the derivation of these parameters.

For FRI parameters, only data generated from the scans taken at TLC level will be used for statistical analyses, but data generated at FRC will also be listed and will be summarised for selected parameters.

Visible airway generations can be different in the pre-dose CT and the post-dose CT scans. For the primary outcome, the airways are trimmed until the same length for both visits. We thus only asses the generations of airways that are visible in the scans of both study visit days. This allows us to view the pure bronchodilation of the airways.

The values of siVaw and siRaw are derived from iVaw and iRaw by dividing iVaw by the image based lobe volume (iVlobe) for siVaw and by multiplying iRaw by iVlobe for siRaw. See the definitions of iVaw, iRaw and iVlobe below. On a lobar scale (RUL: right upper lobe, RML: right middle lobe, RLL: right lower lobe, LUL: left upper lobe, LLL: left lower lobe), these calculations are:

- siVaw LLL = iVaw LLL / iVlobe LLL
- siVaw LUL = iVaw LUL / iVlobe LUL
- siVaw RML = iVaw RML / iVlobe RML
- siVaw RUL = iVaw RUL / iVlobe RUL
- siVaw RLL = iVaw RLL / iVlobe RLL
- siRaw LLL = iRaw LLL * iVlobe LLL
- siRaw LUL = iRaw LUL * iVlobe LUL
- siRaw RML = iRaw RML * iVlobe RML
- siRaw RUL = iRaw RUL * iVlobe RUL
- siRaw RLL = iRaw RLL * iVlobe RLL

Similarly, values can be derived for the Lower Lobe (LL) by first summing iVaw values for LLL and RLL or for the Upper Lobe (UL) by first summing iVaw values for the LUL, RML and RUL. Distal totals can be derived using all 5 lobes. For airflow and resistance parameters a result from the central region of the lung is also provided and this combined with the distal total gives an overall total. For deriving resistance totals, parallel sums of iRaw should be used, by summing the inverse of iRaw values and then inverting again.

For FRI parameters the values for each lobe, the lower lobe total, upper lobe total and overall total will be listed.

3.1.4 Secondary Efficacy Endpoints

3.1.4.1 FRI Parameters

- Airway volume (iVaw): Absolute value at Day 15

  In the CT scans, the airways can be segmented up to the point where no distinction can be made between the intraluminal and alveolar air. This is where the airway diameter is around 1 – 2 mm, typically around the 5th to 10th bifurcation, depending mainly on the disease state of the individual patient. From the resulting model, the central and distal airway volumes can be assessed at individual airways or in different regions.

  The distal airway volume is defined as the segmented airway volume starting from the third bifurcation, that is from the 5 lung lobes without the central region. It is this distal region that will be used in the analyses in this study.

  Visible airway generations can be different in the pre-dose CT and the post-dose CT scans. The iVaw measurements can be performed in two ways: 1) measure of all the generation visible at certain study visit day 2) only asses the generations of airways that are visible in the scans of both pre-dose CT and the post-dose CT scans. The first parameter is called untrimmed iVaw and gives us an idea of the bronchodilation and bronchial recruitment, while the second parameter, called trimmed iVaw, allows us to view the pure bronchodilation. Both iVaw parameters will be analysed.

- Airway resistance (iRaw): Absolute value at Day 15

  The airway resistance (iRaw) is determined using Computational Fluid Dynamics (CFD). During the CFD calculations, the outflow to each lobe is adjusted iteratively for each patient to match the internal flow rate distributions obtained from the segmentation of the CT scans hence iRaw accounts for the patient specific internal airflow distribution which might be greatly altered by the lung disease. Hence, the airflow distribution in the CFD calculation reflects the airflow distribution as derived from the expansion of the lung lobes from FRC to TLC. The iRaw is defined as the total pressure drop over an airway, divided by the flow rate through that airway.

  Visible airway generations can be different in the pre-dose CT and the post-dose CT scans. For iRaw, the airways are trimmed until the same length for both visits. We thus only asses the generations of airways that are visible in the scans of both study visit days.

3.1.4.2 Spirometry Parameters

- Forced expiratory volume in one second (FEV_1): Change from baseline to Day 15 in post-dose FEV_1

  The volume of air exhaled under forced conditions in the first second. Post-dose results will be used. Change from baseline is calculated relative to the subject-average baseline.

3.1.4.3 Body Plethysmography Parameters

- Functional residual capacity (FRC): Change from baseline to Day 15 in post-dose FRC

  The volume in the lungs at the end-expiratory position. Change from baseline is calculated relative to the subject-average baseline.

[redacted]

[redacted]

[redacted]

3.2 Safety Endpoints

The safety assessments include Adverse Events (AEs) and Serious Adverse Events (SAEs) during the study period.

AEs experienced by the subjects will be collected throughout the entire study and will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Only treatment emergent adverse events from the time of randomization onwards will be summarised. AEs will be assigned to the treatment period in which they first occurred. AEs reported as starting during a Washout Period or follow-up period will be assigned to the last treatment received. If an AE has a missing or partial onset date, then unless the stop date of the AE indicates otherwise, this will be considered an on treatment event.

Clinically relevant findings from laboratory, ECG and vital sign parameters will be reported as adverse events. As such these assessments will not be further tabulated.

3.3 Handling of missing data

Data for FRI parameters will be generated across each lobe of the lung. For an individual there may be missing data within certain lobes if for example the subject is missing that lobe or no airways lead to the lobe (giving a volume of zero and infinite airway resistance). If fissures between lobes cannot be distinguished then only a combined estimate across multiple lobes may be produced. Such results from combined lobes will not be used in the analyses. This will be consistent for both periods. Such combined lobe results may however enable totals and sub-totals to be calculated for a patient if the lobes which are combined coincide with those required for relevant regions.

Data from all individually evaluable lobes will be used in the analysis to allow for the estimation of effects at the subject level across all lobes. For patients with lobes that cannot be distinguished the estimates for that lobe are not meaningful for the patient and so they will not contribute, but this will be the case for both periods. Where scans are not evaluable for a single assessment or period this data is assumed to be missing at random.

Where Day 15 assessments are missing data from unscheduled post-baseline assessments will be used in their place, if available. No further imputation for missing values is planned.

4. ANALYSIS METHODS

The primary objective of this study is to assess the effect of treatment with GFF MDI, 14.4/9.6 µg ex actuator, BID relative to Placebo MDI BID on specific image based airway volumes and resistance in subjects with moderate to severe COPD.

4.1 General principles

4.1.1 Hypothesis testing

For the efficacy analyses, the null hypothesis for each pair-wise comparison will be that the mean GFF MDI treatment effect is equal to that of Placebo MDI; the alternative hypothesis is then that the GFF MDI treatment effect and that of Placebo MDI are not equal. P-values will thus be reported as two-sided. Statistical level of significance will be set to 0.05.

For the co-primary endpoints and other FRI parameters the effect is defined using the absolute value at Day 15 of each TP. For the spirometry and plethysmography parameters the effect is defined in terms of the change from baseline, given that these parameters are commonly reported in those terms.

The null (H0) and alternative (H1) hypotheses with µ representing the mean are:

H0: $\mu_{GFF} = \mu_{placebo}$

H1: $\mu_{GFF} \neq \mu_{placebo}$

For each parameter in each group this null hypothesis will be tested. The different groups are:

- Primary efficacy endpoints: FRI
- Secondary efficacy endpoints: FRI; Spirometry and Body Plethysmography
- [redacted]

In order to gain extra insight into the mode of action of the product, additional exploratory analyses may be executed using (robust) linear regression or mixed-models if necessary and reported outside of the Clinical Study Report (CSR).

The Intent-to-Treat (ITT) Population will be considered the primary analysis population for efficacy.

Continuous efficacy variables will be summarized with descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum and maximum). Where data has been logarithmically transformed for analysis the summary statistics on the back-transformed data will include the geometric mean and the coefficient of variation (calculated as $100x\sqrt{[exp(s^2)-1]}$, where s is the standard deviation of the data on the log scale. Categorical variables will be summarized with frequency counts and percentages, by treatment.

Only data deemed to meet acceptability criteria, for example regarding the quality of spirometry procedures, will be listed and summarised.

4.1.2 Control of Type I error

For the primary efficacy endpoints, Hochberg's step-up procedure will be used as multiplicity adjustment. No correction will be performed for the secondary and the other efficacy endpoints.

4.1.3 Software

All statistical analysis will be conducted [redacted]

4.2 Analysis methods

4.2.1 Disposition, demographics and baseline characteristics

Descriptive summaries of disposition, demographics and baseline characteristics will be produced. Disposition tables will summarise the number of patients who received each treatment, the number who completed 1 or 2 treatment periods and the number of early

discontinuations. The number of patients in each analysis set will be summarised along with any reasons for exclusion.

Demographics and baseline characteristics at screening will be summarised descriptively, including COPD disease duration and symptom severity scores. Baseline pre and post bronchodilator spirometry parameters and reversibility to Ventolin HFA will be summarised using descriptive statistics based upon the baseline assessments within each treatment period.

4.2.2 Concomitant medications

Concomitant medications will be will be assigned a preferred term and an ATC (Anatomic Therapeutic Class) term using the latest version of the World Health Organization Drug Dictionary (WHO-DD) available. Medications will be summarised according to whether they are COPD related or non-COPD related. Summaries will be presented for those medications started prior to the beginning of study treatment, those started during a treatment period and those started during the washout period.

4.2.3 Exposure and compliance

The number of days of exposure to each treatment will be defined as ((End date of treatment – Date of first dose of treatment) + 1).

Percent compliance is defined as (total number of puffs of study treatment taken across study days/total expected puffs taken across study days) across all days of a subject's dosing between start of study treatment and last day on study treatment) x 100. 4 puffs a day are expected, with 2 puffs on the final day of treatment.

Exposure to IP, number of puffs/inhalations of IP and % compliance will be summarized by treatment using the safety analysis set.

4.2.4 Analysis of FRI data

The primary analyses will be conducted using the ITT population. Similar methods will be used for the analysis of each of siVaw and siRaw.

The Day 15 value for each parameter in each period will be analysed using a linear mixed effect model. It is anticipated that the data will be logarithmically transformed prior to analysis. A multi-level model will be used to incorporate the repeated measurements from the lobes for each subject.

The model will include fixed effects for period, treatment, lobe and treatment by lobe interaction. The model will not include treatment sequence unless that term is determined to be important ($p<0.10$). Lobe will be included as a random effect, within each subject. Heterogeneity across lobes (within subject) will be modelled using an unstructured variance-covariance matrix, with independence assumed between subjects.

If this model fit fails to converge a compound symmetry covariance structure will be considered to model correlation across lobes from the same patient. If necessary, a per-visit

composite from across all lobes may be formed in order to conduct analyses at the subject rather than the lobe level. This would be based upon a sum across all available lobes for a subject, scaled for the number of evaluable lobes.

Estimates will be produced of the difference between treatments taken across all lobes. Where logarithmic transformations have been made, estimates will be exponentiated and treatment effects presented as ratios. Estimates and standard errors will be reported along with 2-sided 95% confidence intervals and p-values. The Kenward-Roger approximation for degrees of freedom and correction of downward bias in the standard error of fixed effect parameters will be used.

For the primary FRI endpoints only, line-plots will be produced displaying Day1 and Day 15 absolute values by treatment and sequence at the individual patient level using the mean of data from available single lobes for each patient.

For the primary endpoints only, the mITT population will be used to produce sensitivity analyses using only patients with data from both periods without important protocol deviations. Similar mixed models will be used. Should no patients require exclusion then these sensitivity analyses will not be required.

For the primary endpoints only, a further model will be produced which includes covariates for baseline. The model will include fixed effects for period, treatment, lobe and treatment by lobe interaction, subject-average baseline by lobe and period-dependent baseline by lobe. Both versions of baseline are continuous covariates. The use of both subject-average and period-dependent baselines allows for different coefficients for the between and within subject covariate regressions (Kenward and Roger 2010). Period-dependent baselines will be summarised for the primary endpoints.

Similar analyses to the primary analysis will be conducted for secondary and other efficacy endpoints based upon FRI, with the exception of the mass of deposited particles, the Internal Airflow Distribution and Air Trapping. For these values, only descriptive summaries will be produced by showing the deposition in each region of the patient's lungs at baseline. For the Internal Airflow Distribution, the presented values will consist of distance to normal values.

4.2.5 Spirometry / Body Plethysmography data

For spirometry and body plethysmography parameters data will be at the subject level and not split by lobe. The change from baseline to Day 15 for each endpoint will be analysed using a linear mixed effect model including subject-average baseline as a continuous covariate and treatment and period as fixed effects. The model will not include treatment sequence unless that term is determined to be important ($p<0.10$). The ITT population will be used. It is expected that plethysmography endpoints may require logarithmic transformation, but that spirometry endpoints will not.

4.2.6 Assumptions Checks and Removal of Outliers in Sensitivity Analyses

It is expected that logarithmic transformations will be required for most FRI and plethysmography endpoints, with the exception of the percent predicted lobe volume. Data

will be transformed via the natural logarithm prior to analysis and the adjusted mean estimates and confidence intervals from the linear models will be exponentiated back for presentation. As such the treatment effect for these endpoints will be presented as a ratio.

Under certain circumstances, (eg, during a COPD exacerbation unrelated to treatment) extreme and atypical values can arise. Such values may disproportionately affect model-based estimates of the fixed effect and variance parameters. Depending on the plots of the standardized residuals versus fitted values of the mixed-effect models, other data transformations may be considered. If necessary, this may include the fifth root, adapted for positive and negative values: fifthroot (x) = sign (x) * (abs (x)) ^ (1/5).

For resistance measures, outliers can occur that are real values but affect the model estimates extremely. In these cases, values that are larger than the third quantile + 3 times the interquartile range may be removed. Infinite values for resistance are possible and these will be listed, but will be removed from the data before statistical analysis. If erroneous values are detected, every effort will be made to correct them prior to database lock. However, if these values cannot be corrected, they will be considered for removal from the analysis.

4.2.7 Exploratory analyses

[redacted]

4.2.8 Safety data

Adverse events will be summarized by the number and percentage of subjects experiencing an event. Tables will show the overall incidence of AEs, and the incidence for each treatment. Treatment emergent adverse events from the time of randomization onwards will be summarised. AEs reported as starting during a Washout Period or follow-up period will be assigned to the last treatment received.

AEs will be presented according to MedDRA preferred term and system organ class. Summaries will be produced by severity, seriousness, AEs leading to discontinuation, and by causality assessment to study drug. No hypothesis tests will be performed.

Clinically relevant findings from laboratory, ECG and vital sign parameters will be reported as adverse events. As such these assessments will not be further tabulated.

5. INTERIM ANALYSES (NOT APPLICABLE)

No interim analyses are planned in this study.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The clinical study protocol stated that all FRI, spirometry and body plethysmography endpoints would utilise changes from baseline for statistical analyses. Effects were defined as differences between Day 15 and Day 1. As described in Kenward and Roger, conditioning on period-dependent baselines in a cross-over study has the potential to increase the variability of treatment effect estimates (Kenward and Roger 2010). For this reason statistical analyses will now be conducted either using absolute values or relative to subject-average (period independent) baselines.

It is now planned that FRI endpoints will be analysed using their absolute values at Day 15 rather than the change from baseline. This avoids the need to derive baselines across multiple lobes. In a cross-over study comparisons are driven by within-subject comparisons and the adjustment for baselines is not necessary as this adjusts for between patient variability.

Spirometry and plethysmography endpoints will utilise change from a subject-average baseline. The use of the subject-average baseline covariate will not affect the treatment effect estimates, but will allow for the estimation of changes from baseline for each separate treatment.

Given that the ITT, mITT and safety populations are expected to only differ slightly demographics and other characteristics will only be summarised for the ITT population. The mITT population will purely be used for sensitivity analyses of the primary endpoints should the ITT and mITT populations differ.

7. REFERENCES

[redacted]

De Backer L, Vos W, De Backer J, Van Holsbeke C, Vinchurkar S, De Backer W. The acute effect of budesonide/formoterol in COPD: a multi-slice computed tomography and lung function study. Eur Respir J. 2012 Aug 1;40(2):298–305.

Kenward MG, Roger JH. The use of baseline covariates in crossover studies. Biostatistics (2010), 11, 1, 1–17

8. APPENDIX