NCT03888131

STATISTICAL ANALYSIS PLAN

STUDY CODE No.: CCD-01535AC1-02

A 24-week, double blind, double dummy, randomized, multicentre, 2-arm parallel group, active controlled clinical trial of fixed combination of beclometasone dipropionate plus formoterol fumarate administered via pMDI (CHF 1535) versus the fixed combination of budesonide plus formoterol fumarate (Symbicort® Turbohaler®) in patients with Chronic Obstructive Pulmonary Disease

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Author:	PPD

Contents

List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical classification
BD	Bronchodilator
BDP	Beclometasone dipropionate
βhCG	Beta-Human Chorionic Gonadotrophin
b.i.d.	*Bis In Die* (twice a day)
BUD	Budesonide
CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CSP	Clinical Study Protocol
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
DBP	Diastolic Blood Pressure
DRM	Data Review Meeting
DRR	Data Review Report
ECG	Electrocardiogram
ETV	Early Termination Visit
FEV_1	Forced Expiratory Volume in the first second
FF	Formoterol Fumarate
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	Heart Rate
IC	Inspiratory Capacity
ICS	Inhaled corticosteroid
ITT	Intention to Treat
LABA	Long-acting β2 agonist
LAMA	Long-acting muscarinic antagonist
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MMEF	Maximal Mid-Expiratory Flow
MMRM	Mixed Model for Repeated Measures
PDF	Portable Focument Format
pMDI	pressurised Metered Dose Inhaler
PP	Per-Protocol
PR	Time interval between the beginning of the P wave and the beginning of the QRS complex in ECG
PRO	Patient Reported Outcomes
PT	Preferred Term
QRS	Time Interval Between the Q and R and S wave in the ECG
QTc	Time interval between the Q and T waves in the ECG (corrected for HR)
QTcF	Fridericia – Corrected QTc
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGRQ	Saint George's Respiratory Questionnaire
SI	International System of Units
SOC	System Organ Class

WHO	World Health Organization

VERSION HISTORY

Version	Date	Change History
0.1	22 November 2018	First version
0.2	31 December 2018	Second version (after internal review)
0.3	08 November 2019	Third version (after internal review)
0.4	30 March 2020	Fourth version (after internal review)
1.0	21 December 2020	Final Version
2.0	29 July 2022	Updated version. The following changes were implemented: • Section 7.3: Addition of a clarification to reinforce the validity of the Missing At Random assumption in handling COVID-19 related missing data. • Section 7.3: addition of rules to handle missing data for procedures • Section 7.8.6: clarification on IC parameter • Section 7.8.7: clarification on QTcF parameter • Section 7.10.1.4: clarification about ECG data exclusion due to PR parameter value = 0 • Sections 8.1.2 – 9.2.11: update on Kaplan-Meier periods definition • Section 9.1: p-value for non-inferiority added • Section 9.2.10: update on algorithm for COPD exacerbations to be considered as a single episode. • Section 10.4: clarification on summary statistics for ECG data and update on QTcF abnormality categories • Section 12.0: Reclassification of regions based on official source: https://en.wikipedia.org/wiki/List_of_regions_of_China • Section 16: updates in the list of tables and listings. • Correction of typos in the document

1 Introduction

This document presents the Statistical Analysis Plan (SAP) for Chiesi Farmaceutici S.p.A. protocol CCD-01535AC1-02: "A 24-week, double blind, double dummy, randomized, multicentre, 2-arm parallel group, active controlled clinical trial of fixed combination of beclometasone dipropionate plus formoterol fumarate administered via pMDI (CHF 1535) versus the fixed combination of budesonide plus formoterol fumarate (Symbicort® Turbohaler®) in patients with Chronic Obstructive Pulmonary Disease".

This analysis plan is based on the final protocol (version 1.0, dated 09 November 2017), the final electronic case report form (eCRF) (version 3.0, dated 12 April 2019), the final diary for patient reported outcomes (version 2.0, dated 24 January 2018) and the External Spirometry data (DTS version 2.0, dated 21 November 2018).

The SAP provides the description of the final analyses. In case of deviations from the SAP, explanations will be provided in the Clinical Study Report (CSR).

2 Study Design

This is a phase III, double-blind, double-dummy, randomised, multicentre, 2-arm parallel-group, active-controlled study in approximately 750 randomised patients. Approximately 50 sites will be involved.

During the run-in period, all patients will receive Symbicort® Turbohaler® 160/4.5 µg per inhalation, 2 inhalations b.i.d. (daily delivered dose of Budesonide (BUD) 640 µg plus Formoterol Fumarate (FF) 18 µg).

Eligible patients will then be randomised to one of the two following treatments:

- **Treatment A (Test Product):**
  - 2 inhalations of CHF 1535 100/6 µg pMDI plus matched placebo of Symbicort® Turbohaler® 2 inhalations in the morning AND
  - 2 inhalations of CHF 1535 100/6 µg pMDI plus matched placebo of Symbicort® Turbohaler® 2 inhalations in the evening

  (total daily metered dose: BDP 400 µg plus FF 24 µg).

- **Treatment B (Reference Product):**
  - 2 inhalations of Symbicort® Turbohaler® 160/4.5 µg/unit dose plus matched placebo of CHF 1535 pMDI 2 inhalations in the morning AND
  - 2 inhalations of Symbicort® Turbohaler® 160/4.5 µg/unit dose plus matched placebo of CHF 1535 pMDI 2 inhalations in the evening

  (total daily delivered dose: BUD 640 µg plus FF 18 µg)

The study plan and scheduled tests are described and summarised in the section 7.1 of Clinical Study Protocol (CSP).

3 Study Objectives

3.1 Primary Objective

- To demonstrate that CHF 1535 pMDI is non-inferior to Symbicort® Turbohaler® in terms of pulmonary function (change from baseline in pre-dose morning FEV_1 at week 24) in patients with COPD

3.2 Secondary Objectives

- To evaluate the effect of CHF 1535 pMDI on other lung function parameters, and patient reported outcomes (PROs).
- To assess the safety and the tolerability of the study treatments

4 Study Variables

4.1 Efficacy Variables

4.1.1 Primary Efficacy Variable

- Change from baseline in pre-dose morning FEV_1 at Week 24

4.1.2 Secondary Efficacy Variables

- Change from baseline in pre-dose morning FEV_1 at all the other clinic visits
- FEV_1 response (change from baseline in pre-dose morning $FEV_1 \geq 100$ ml) at Week 24
- Change from baseline in pre-dose morning FVC and IC at all clinic visits
- Change from baseline in pre-dose Maximal Mid-Expiratory Flow (MMEF) at all clinic visits
- Change from baseline in the SGRQ total score and domain scores at Week 12 and Week 24
- Change from baseline in COPD Assessment Test (CAT) at all clinic visits
- Change from baseline to each inter-visit period and to the entire treatment period in the percentage of days without intake of rescue medication and in the average use of rescue medication (number of puffs/day)
- Time to first moderate or severe COPD exacerbation
- Rate of moderate and severe COPD exacerbations over 24 weeks of treatment

4.2 Safety Variables

- Adverse Events (AEs) and Adverse Drug Reactions (ADRs)
- Vital signs: systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate at all clinic visits
- 12-lead ECG parameters: heart rate (HR), PR, QRS, QTcF at Visit 1 and Visit 6
- Standard Haematology and Blood Chemistry at Visit 1 and Visit 6

4.3 Other Variables

No other variables defined.

5 Sample Size

The sample size has been calculated to demonstrate the non-inferiority of CHF 1535 pMDI over Symbicort® Turbohaler® in terms of change from baseline in pre-dose morning FEV_1 at Week 24 in the Chinese population.

A total of 540 completed and evaluable patients in the Per Protocol (PP) set (270 per group) will provide approximately 90% power to demonstrate the non-inferiority of CHF 1535 versus Symbicort in pre-dose morning FEV_1 at Week 24, with a non-inferiority margin of -0.07L and a one-sided significance level of 0.025, assuming no difference between treatments and a standard deviation of 250 ml. Estimating a drop-out rate of 20% and a percentage of completed patients with major protocol deviations of 10%, a total of 750 patients (375 per group) will be randomised.

6 Analysis Sets

The definitions of the analysis sets are summarised below. A final agreement on the patients to be included in or excluded from each analysis set will be reached during the Data Review Meeting (DRM), before breaking the blind. Inclusions and exclusions from analysis sets will be fully documented in the Data Review Report (DRR).

In case an error occurs in treatment allocation, the following rule will be followed. If a patient was randomised but received the incorrect treatment:

- the patient will be reported under the randomised treatment group for all analyses performed on the Randomised Set and on the ITT Set (and in listings on all screened patients);
- the patient will be reported under the randomised treatment group for all analyses performed on the PP set. However, in case of relevant duration of the period affected by treatment misallocation, the patient will be excluded from the PP set;
- the patient will be reported under the treatment actually received for all analyses performed on the Safety population (i.e. an as-treated analysis will be performed). In case of treatment misallocation affecting only a specific period of the study, the patient will be reported under the treatment actually received for >50% of the duration of the randomised treatment period of the patient.

All the cases of treatment misallocation will be discussed during the DRM and the decisions on the inclusion of analysis sets will be documented in the Data Review Report (DRR).

6.1 Safety Set

All randomized patients who receive at least one administration of the study medication.

6.2 Intention-to-Treat Set

All randomized patients who receive at least one administration of the study medication and with at least one available evaluation of efficacy after the baseline.

6.3 Per Protocol Set

All patients from the ITT set without any major protocol deviations (e.g., wrong inclusions, poor compliance, forbidden concomitant medications). Exact definition of major protocol

deviations will be discussed by the clinical team case by case during the blind DRM and described in the DRR.

6.4 Other Sets Defined for Tables and Listings

For the purposes of tables and listings, the following sets are also defined:

- Enrolled Set: all patients who provided informed consent for the study;
- Randomised Set: all patients randomised to study medication.

7 General Considerations for Statistical Analysis

7.1 Statistical Significance

All tests of hypotheses will be two-sided and conducted at the 0.05 significance level, and all confidence intervals will be two-sided at the 95% confidence level (with the only exception of mean changes from baseline in 12-lead ECG parameters, for which two-sided intervals at the 90% confidence level will be presented).

7.2 Multiplicity

No multiplicity adjustment will be performed in this study.

7.3 Handling of Missing Data

Missing values for statistical analysis

- ✓ For the primary and secondary efficacy variables measured repeatedly over time (change from baseline), a linear mixed model for repeated measures (MMRM) will be used to handle missing data. Under the missing at random (MAR) assumption, these models provide an unbiased estimate of the treatment effect that would have been observed if all patients had continued on treatment for the full study duration [1]. This means that the MAR assumption in a non-inferiority study is a conservative approach because it does not favour the non-inferiority hypothesis. Moreover, the MAR assumption is also applicable for the subjects who discontinue the study due to reasons directly or indirectly related to COVID-19 pandemic (for example: early withdrawal because of patient refusal to go to the hospital due to COVID-19 pandemic or restricted by COVID-19 outbreak). As mentioned also in a recent paper by Meyer et al "most data that are missing due to pandemic reasons may be argued to be MCAR or MAR, especially if missingness is due to structural reasons" [3].
- ✓ Secondary efficacy analysis of the moderate and severe COPD exacerbation rate will be based on a negative binomial model. The validity of this model relies on the MAR assumption.
- ✓ In the FEV_1 responder analyses, patients with missing data for pre-dose FEV_1 at Week 24 will be considered as non-responders. Patients with missing baseline value for pre-dose FEV_1 will also be considered as non-responders. For non-responders due to missing data with a missing baseline value (i.e., with baseline value still missing after having applied ad-hoc rules potentially defined in the DRR), it will be imputed as the overall mean baseline value (considering patients from both treatment groups with available baseline value in the relevant analysis set). This will allow the inclusion of all patients in the statistical analysis.

Missing values for descriptive statistics

- ✓ The number of patients with missing data will be presented under a "Missing" category. Unless otherwise stated, missing values will be included in the denominator count when computing percentages.
- ✓ When continuous data are being summarised, only the non-missing values will be evaluated for computing summary statistics.

Missing values for diary data

- ✓ A minimum of 14 days with available measurements will be required in each inter-visit period (including run-in period) and in the entire randomised treatment period to consider the following variables as non-missing: percentage of days without intake of rescue medication and average use of rescue medication.

Missing values for dates

- ✓ In order to calculate the duration of smoking, the following rules will be applied for the partial dates of start/stop of smoking:
  - if only the day of start date or stop date is missing, the first day of the month will be assumed;
  - if the day and month of start date or stop date is missing, January 1st will be assumed.
- ✓ In order to calculate the time since first COPD diagnosis, the following rules will be applied for partial dates of first COPD diagnosis:
  - if only the day is missing, the first day of the month will be assumed;
  - if the day and the month are missing, January 1st will be assumed.
- ✓ In order to calculate the time since last COPD exacerbation, the following rules will be applied for the partial dates of last COPD exacerbation:
  - if only the day is missing, the first day of the month will be assumed;
  - if the day and month of start date are missing, January 1st will be assumed.
- ✓ In case of missing or incomplete dates not directly allowing allocation to any of the four categories of medications, a worst-case allocation will be done according to the available parts of the start and the end dates, allocating the medication to the first category allowed by all available data, according to the following order.
  - concomitant medication;
  - medication maintained during the randomised treatment period;
  - post-treatment medication;
  - previous medication.
- ✓ In case of missing or incomplete dates not directly allowing allocation to any of the four categories of procedures, a worst-case allocation will be done according to the available parts of the start and the end dates, allocating the procedure to the first category allowed by all available data, according to the following order.

- concomitant procedure;
- procedure maintained during the randomised treatment period;
- post-treatment procedure;
- previous procedure.

✓ In case of missing or incomplete dates not directly allowing allocation to any of the categories of AEs, a worst-case allocation will be done according to the available parts of the start and the stop dates. The AE will be allocated to the first category allowed by the available data, according to the following order:

- treatment emergent;
- post-treatment;
- pre-treatment.

Missing values for questionnaires

✓ The domain scores of the SGRQ will be considered non-missing if the following conditions will be satisfied:

- Symptoms score: missing items ≤ 2; the weight for the missed item is subtracted from the total possible weight for the Symptoms domain (662.5) and from the Total weight (3989.4)
- Activity score: missing items ≤ 4; the weight for the missed item is subtracted from the total possible weight for the Activity domain (1209.1) and from the Total weight (3989.4).
- Impacts score: missing items ≤ 6. The weight for the missed item is subtracted from the total possible weight for the Impacts domain (2117.8) and from the Total weight (3989.4).
- If at least one domain score will be missing, the total score will be considered as missing.

✓ The COPD Assessment Test (CAT) total score will be considered as missing in case at least one of the eight questions is missing.

Missing values for COPD exacerbations

✓ Only COPD exacerbations with onset during the randomised treatment period (i.e., with date of start of randomised treatment period ≤ onset date ≤ date of end of randomised treatment period) will be included in the analysis.

✓ In case of partial onset date of COPD exacerbation due to missing day, the onset of the event will be assumed as the first day of the month in the analysis of time to first COPD exacerbation. If partial onset date of COPD exacerbation is in the month of date of first randomised study medication intake, the date of first randomised study medication intake will be considered as onset date of the event.

✓ In case of emergency room admission/hospitalization for COPD exacerbation, the following rules will be applied in the calculation of the length of stay:

- if the minutes of the time of admission or discharge are missing, :00 will be assumed;

- if the hours are missing for the time of admission and/or discharge, the length of stay will be assumed as 24 hours * (date of discharge – date of admission). If date of discharge is equal to date of admission, the length of stay will be assumed 24 hours.

Missing values for 12-lead ECG

✓ 12-lead ECGs should be performed in triplicate and in the analyses the average of the triplicate values will be used. If less than three measurements will be available, the average of the available measurements will be considered.

Other critical missing data, if any, will be discussed during the DRM and fully documented in the DRR.

7.4 Covariates

All statistical models (MMRM, Cox model, negative binomial model and logistic model) will include treatment, region, number of COPD exacerbations in the previous year (1, >1), severity of airflow limitation at screening (post-bronchodilator FEV_1 % of predicted normal value at screening <30%, ≥30%) and smoking status at screening visit (ex-smoker, current smoker) as fixed effects.

The MMRM will also include visit/inter-visit period, the treatment by visit/inter-visit period interaction, the baseline value and the baseline by visit/inter-visit period interaction as covariates.

For sensitivity analysis, the linear MMRM will be repeated by including also the COVID-19 variable ("N" or "Y") as fixed effect (defined in section 7.13.1).

An unstructured covariance matrix will be assumed in the MMRM. If the model fails to achieve convergence with an unstructured covariance matrix, the following structures will be applied in the following order: first-order antedependence (ANTE(1)), heterogeneous first-order autoregressive (ARH(1)), first-order autoregressive (AR(1)), Toeplitz (TOEP), heterogeneous compound symmetry (CSH), compound symmetry (CS).

The negative binomial model will also include log-time on study as an offset. The logistic model will also include the baseline value as a covariate.

The calculation of the adjusted means (least squares means) will be based on:

- coefficients for classification effects (i.e., the effects of categorical covariates) proportional to the margins observed in the group of patients analysed;
- effects of quantitative covariates set equal to their mean values in the group of patients analysed.

In the analyses stratified by one of the factors included in the statistical model used for the non-stratified analysis, the factor will be removed from the model (e.g., in the analysis stratified by the smoking status, the smoking status will not be included as a factor in the model).

Due to a relevant number of sites that could have a limited number of randomised patients (i.e., lower than 10) included in the ITT set, the sites have been grouped on the basis of their regional proximity. In all statistical models the factor "site" will be replaced by the factor "region". Criteria for the identification of the regions are reported in section 12.

7.5 Interim Analyses

No interim analysis will be performed.

7.6 Examinations of Subgroups

As exploratory purpose, the analysis of the primary efficacy variable will be also performed on the ITT set stratifying by:

- Smoking Status at screening (ex-smoker, current smoker)
- Severity of airflow limitation (post-bronchodilator FEV_1 % of predicted normal value at screening <30%, ≥30%)
- Number of COPD exacerbations in the previous year (1, >1)

Primary efficacy variable will also be evaluated in subgroups of patients "before" or "during" COVID-19 outbreak.

7.7 Descriptive Statistics

Descriptive statistics for quantitative variables will include n (the number of non-missing values), arithmetic mean, standard deviation (SD), median, minimum, maximum values, and the 95% or 90% confidence interval (CI) of the arithmetic mean. The 1st and the 3rd quartiles will also be presented for the total SGRQ score and domains and for the CAT score.
Categorical variables will be summarised by using frequency count and percent distributions. Unless otherwise stated, percentages will be calculated using the total number of patients per treatment/population.

7.8 Definitions

7.8.1 Baseline and Change from Baseline

The baseline value for each efficacy and safety variable is defined as follows:

- For variable recorded at clinic visit, the baseline is the value recorded at Visit 2, or at Visit 1 for variables not recorded at Visit 2 (ECG and laboratory parameters).
- For all the derived efficacy variables from daily diary data, the baseline:
  - will be calculated if there are at least 14 available assessments in the entire run-in period;
  - will not be calculated otherwise and will be set at missing.

Additional specifications for the calculation of baseline value for each efficacy and safety variables are reported in the relevant sections in chapters 9 and 10.

For each of the above variable, **change from baseline** is defined at each visit (or at each inter-visit period/entire treatment period for the variables derived from diary data) as:

value at the visit (or inter-visit period/entire treatment period) – baseline value.

7.8.2 Date of First and Last Randomised Study Medication Intake

The date of first randomised study medication intake is the earliest date of randomised study medication intake considering the eCRF data, corresponding to the date part of the variable RFSTDTC in the SDTM dataset DM.

The last randomised study medication intake is the date of last study medication intake recorded in the Study Termination Form of the eCRF. This variable corresponds to the date part of the variable RFENDTC in the SDTM dataset DM.

7.8.3 Study Day

The study day relative to the first randomised study medication intake will be calculated as:

- date of event – date of start of randomised treatment period + 1 (if date of event ≥ date of start of randomised treatment period);

or

- date of event – date of start of randomised treatment period (if date of event < date of start of randomised treatment period).

7.8.4 Visit dates

For each visit, the date recorded by the Investigator in the eCRF (variable SVSTDTC in the SDTM SV dataset) will be considered as the visit date in all the algorithms and the listings.

7.8.5 Date of Start/End of Randomised Treatment Period

Since many algorithms used in the statistical analyses require the start and/or the end of the randomised treatment period to be identified, ad-hoc variables specifying these dates will be defined.

- In general, the date of start of randomised treatment period should coincide with the date of Visit 2, the randomisation date and the date of first randomised study medication intake. However, discrepancies between these dates may arise and the most appropriate date to be used in such situations requires a case-by-case evaluation. The date of start of randomised treatment period will be initially set equal to the date of first randomised study medication intake for all patients. The need for deviations from this rule in single cases will be evaluated during the DRM and documented in the DRR.
- The date of end of randomised treatment period will be initially set according to the following rule:
    - If Visit 6 or early termination visit was performed, then the date of end of randomised treatment period will be set equal to the date of Visit 6 or date of early termination visit;
    - If Visit 6 or early termination visit was not performed, then the date of end of randomised treatment period will be defined as max[dates of clinic visits (including unscheduled visits), date of last randomised study medication intake (as per section 7.8.2)];

The need for deviations from these rules in single cases will be evaluated during the DRM and documented in the DRR.

7.8.6 Clarification on IC parameter

As per protocol, for the IC parameter the highest value from three technically satisfactory attempts should be recorded in the database.

However, in the ATS guideline "Standardization of Spirometry 2019 Update", it is reported that IC parameter should be recorded as average value of the acceptable efforts: "*For IC, the average value from the acceptable maneuvers should be reported*.".
Therefore, for this study, the average value of IC data is recorded in the database.

7.8.7 Clarification on QTcF

According to the protocol, QTcF was required to be provided automatically by the ECG machine, but it was discovered that local ECG machines used at site did not provide it and it was then manually calculated by investigators.
To avoid calculation and entry errors, QTcF will be re-derived in ADaM for each replicate and then averaged. The following formula, as reported in the protocol, will be used:

$$\text{Fridericia-corrected QTc} = QT/\sqrt[3]{RR}$$

And, since RR interval is not collected in the eCRF, the following formula will be used:

$$RR = 60/HR$$

Re-derived averaged values will then be used for analysis and reporting. Original values will only be stored in SDTM.

7.9 Data Re-allocation

The following rules on data re-allocation will be considered:

- 12-lead ECG and laboratory data (haematology, blood chemistry and serum pregnancy test) recorded at the study termination visit for discontinued patients will be always re-allocated to Visit 6.
- Data collected at multiple visits (spirometry, SGRQ, CAT test, weight, smoking status, vital signs) and recorded at the early termination visit for discontinued patients will be re-allocated by selecting the planned theoretical visit following the last one performed before the early termination visit with the expected theoretical date closest to the date of the early termination visit. For example, if the last visit performed before the early termination visit was Visit 3, the data recorded at the study termination visit will be re-allocated to Visit 4, 5 or 6 depending on the date of the early termination visit. If the early termination visit is equidistant between two planned theoretical visits, the latest of the two possible planned theoretical visits will be selected. If the early termination visit was performed less than 7 days after the preceding visit, data recorded at the study termination visit will not be re-allocated and they will be excluded from the statistical analysis. For each assessment, only the visits at which the assessment was scheduled will be considered for re-allocation; this means that SGRQ data can be re-allocated only to Visits 4 and 6.
- For discontinued patients, efficacy data recorded in the diaries from the last visit performed before the early termination visit or the date of discontinuation onwards will be reallocated to the next expected inter-visit period;
- for discontinued patients, study medication intake data recorded in the diaries from the last visit performed before the date of last randomised study medication intake onwards will be reallocated to the next expected inter-visit period;

- in case of missing intermediate visit not due to the re-allocation of data collected at the early termination visit (e.g., Visit 4 missing, but Visits 3 and 5 performed), the expected date for the missing intermediate visit will be derived through the following algorithm:
    - the number of days between the last available visit before the missing intermediate visit and the first available visit after the missing intermediate visit will be calculated according to the expected fraction of days between visits as per protocol.
    - the date for the missing intermediate visit will be calculated as: date of the visit before the missing intermediate visit + the integer part of the result derived at the previous bullet point.

  This algorithm can be easily applied when more than one intermediate visit is missing. Below a couple of examples:

  Example 1: one intermediate visit missing (V4)
  Date V3: 3 Apr
  Date V5: 9 Jul
  Date V5 – Date V3 = 97 days
  *Date V4 (imputed) = Date V3 + 8/14*97days = 28 May*
  Date V5 - Date V4 (imputed) = 42 days

  Example 2: two intermediate visits missing (V4 and V5)
  Date V3: 3 Apr
  Date V6: 20 Aug
  Date V6 – Date V3 = 139 days
  *Date V4 (imputed) = Date V3 + 8/20*139 days = 28 May*
  *Date V5 (imputed) = Date V4 (imputed) + 6/20*139 days = 8 Jul*
  Date V6 - Date V5 (imputed) = 47 days

The following rules to handle unscheduled/optional assessments taken on the same date of a scheduled visit (i.e. Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6) or rescheduled Visit 1.1 will be considered:

- two or more spirometry measurements valid for the same timepoint (i.e., predose, with the timepoint checked vs. the time of medication intake):
    - FEV_1: the highest value from the measurements with Best Test Review (BTR) grade "acceptable" or "borderline acceptable" will be considered. If BTR grade = "unacceptable" for all measurements, the highest value will be considered;
    - FVC: same approach as for FEV_1;
    - FEV_1/FVC: re-calculated considered the FEV_1 and FVC values determined as above described;
    - for post-salbutamol spirometry at Visit 1 / re-scheduled Visit 1, the assessment originally flagged as "post-dose" will always be used also in case of additional post-salbutamol measurements. The rationale for this exception is that the original values were considered for the assessments of eligibility;
- 12-lead ECG:
    - in case of multiple measurements associated to the same timepoint (with the timepoint checked vs. the time of medication intake), the average value will be considered for HR, QTcF, PR and QRS;

- Vital signs:
    - in case of multiple measurements associated to the same timepoint (with the timepoint checked vs. the time of medication intake), the average value will be considered for SBP and DBP;

The following rules to handle unscheduled/optional assessments during run-in period will be considered:

- 12-lead ECG:
    - the last pre-dose assessment before Visit 2 with non-missing result will be considered in the analysis as the Visit 1 ECG;
- Laboratories:
    - the last assessment before Visit 2 of each parameter should be considered as from Visit 1 in the analysis. For White Blood Cells and the differential count parameters (lymphocytes, neutrophils, monocytes, eosinophils, basophils) the last complete assessment (i.e., with available measurements for all these parameters) before Visit 2 should be considered in the analysis. If no complete assessment is available, the last assessment before Visit 2 with the highest number of available parameters should be considered in the analysis.

In general, any potential issues of the approaches above defined will be evaluated during the DRM and documented in the DRR. All the calculations for analyses (descriptive and inferential) will be done after re-allocation of data.

7.10 Exclusion of Data from the Statistical Analyses

7.10.1 Exclusion of Data from All Statistical Analyses

7.10.1.1 Spirometry parameters

Spirometries graded as unacceptable by the centralised BTR process (i.e., with BTR grade = unacceptable) but considered as acceptable by the investigator will not be excluded from the statistical analysis based on this quality assessment. This follows the approach recommended by the paper by Hankinson et al. (*European Respiratory Journal* 2015)[2], where it was concluded that quality assessment regarding the acceptability of individual blows should be primarily used as an aid to assess good quality during testing rather than a reason to subsequently disregard data.

7.10.1.2 Screening re-test for spirometry

If inclusion criteria no. 4 was not met at Visit 1, spirometry measurements will be repeated at Visit 1.1. These repeated measurements will be considered as the Visit 1 assessment in all the analyses (including the definition of the strata and the covariate associated to the severity of airflow limitation). In the listings both Visit 1 and Visit 1.1 assessments will be listed, by flagging the assessment used for the analysis.

7.10.1.3 Diary data

The data recorded in the paper diaries after the date of end of randomised treatment period will not be considered in the calculation of compliance and the diary derived variables.

If "date of end of randomised treatment period" = "Date of Visit 6", the evening session of this date, if present, will also be discarded in the calculation of compliance and the diary derived variables.

In case of duplicate diary data (more than one set of answers on the same session/day), the set of answers entered last will be considered in the analysis.

The run-in period for diary data is defined from the evening session of date of Visit 1 to the morning session of the date of start of randomised treatment period (both inclusive).

The randomised treatment period for diary data is defined from the evening session of date of start of randomised treatment period to the date of end of randomised treatment period.

These period definitions apply to all derived variables from diary data.

7.10.1.4 12-lead ECG numerical parameters

12-lead ECG numerical parameters (HR, QTcF, PR and QRS) from patients with a pacemaker or with atrial fibrillation will not be included in the statistical analysis:

- Patients with a pacemaker inserted before study entry will be identified by the presence of at least one of the following Preferred Terms in the medical/surgical history or concomitant diseases: "Cardiac pacemaker battery replacement", "Cardiac pacemaker evaluation", "Cardiac pacemaker insertion", "Cardiac pacemaker replacement", "Electrocardiogram pacemaker spike", "Pacemaker generated arrhythmia", "Pacemaker generated rhythm", "Pacemaker syndrome", "Cardiac assistant device user" or any other Terms that includes "pacemaker".
- Patients with a pacemaker inserted during study will be identified by the presence of the Preferred Term "Cardiac pacemaker insertion" in the procedures (other relevant cases may be identified during DRM). In these cases, data will be excluded from the analysis from the day of pacemaker insertion onwards.
- Patients with atrial fibrillation will be identified by the presence of at least one of the following Preferred Terms in the concomitant diseases: "Atrial fibrillation", "Cardiac fibrillation".

At each visit, all 12-lead ECG numerical parameters will be also excluded from the statistical analysis if PR = 0 (since this is an indication of an unreliable ECG). If several ECGs are available in the visit (due to triplicate or optional/unscheduled assessments), only the ones with PR = 0 will be excluded.

Regarding the 12-lead ECG, it should be highlighted that the rules above defined will apply only to numerical parameters (HR, QTcF, PR and QRS), while no exclusion of data on abnormalities for investigator's interpretation will be performed (e.g., in case of atrial fibrillation, the occurrence of this abnormality will be considered in the statistical analysis, while the numerical parameters measured at the same visit will be excluded).
A final confirmation of ECG abnormalities leading to exclusion of ECG parameters measured at a specific visit from the statistical analysis will be made during DRM.

7.10.1.5 Derived variables

In case of data excluded from the statistical analysis, the derived variables based on these data will not be calculated. For example, the change from baseline to Visit 5 will not be calculated if the measurement at Visit 5 is excluded from the statistical analysis, or all the changes from baseline will not be calculated if the baseline measurement is excluded.

7.10.2 Exclusion of Data from Per Protocol Analyses

In case of major protocol deviation, the patient will be excluded from the PP set and therefore from all PP analyses. In case of local major protocol deviation, only the affected data at the specific timepoint/visit will be excluded from the PP analyses.

The exclusion of a measurement from the PP analysis will lead to the exclusion of the derived variables based on this measurement from the PP analysis. For example, the change from baseline to Visit 5 will be excluded from the PP analysis if the measurement at Visit 5 is excluded, or all the changes from baseline will be excluded if the baseline measurement is excluded.

7.11 Listings

All data collected in the eCRF will be presented in the listings.

All the variables derived from the diaries and used in the analyses will be presented in the listings. Daily diary data will not be included in the listings, but they will be available in the SDTM datasets.

7.12 Coding

Medical and surgical history, concomitant diseases, procedures and adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0. Medications will be coded using the World Health Organisation Drug Dictionary (WHO-DD), version January 2018.

7.13 Other considerations: Handling impact of COVID-19 Pandemic

At the time of the beginning of the COVID-19 pandemic in China there was no guideline to face the impact of the pandemic on methodological aspects of ongoing trials. Since it was foreseeable that the COVID-19 pandemic would have interfered with the conduct of the trial, on the 31st January 2020 the Sponsor defined some rules to address the possible issues related to pandemic.

The main rules are the following:

- Extension of run-in period with a resupply of the run-in kit when necessary in order to perform the Randomisation visit (V2) at the site the earlier possible.
- Post-randomisation clinic visits (V3 to V5) can be postponed, otherwise the visit should be performed remotely by means a phone call.
- Completion study visit V6 can be postponed until 3 weeks after the expected date of visit, otherwise the patient should be discontinued.
- Study medication, rescue medication and paper diary delivered at patient home.

7.13.1 Handling impact of COVID-19 Pandemic in the Statistical Analysis

All deviations related to the COVID-19 pandemic will be captured and discussed during the DRM and decisions will be documented in the DRR.

Additional analyses have been planned to investigate whether the COVID-19 pandemic impacted on the measurement of the primary efficacy variable.

The date of 31st January 2020, as mentioned above, identifies the group of patients that completed their study period before the implementation of the measures due to COVID-19 outbreak (date of completion/discontinuation before or equal to 31st January 2020). Considering that at the time of the finalisation of the present document (December 2020) emergency due to COVID-19 is still ongoing worldwide and that the containment measures are still active in some sites, no date of end of containment measure is estimable. Therefore only two phases (pre/during pandemic) have been taken into consideration and only two groups were finally defined as follows:

- patients whose study participation was not affected by COVID-19 outbreak (study participation completed before 31st January 2020 included);
- patients whose study participation was potentially affected by COVID-19 outbreak (study participation completed after 31st January 2020).

Sensitivity and subgroup analysis have been planned on primary efficacy variable. Upfront it can be stated that:

- significant impact is expected on spirometry and questionnaires (ie., CAT and SGRQ) endpoints. For patients that replaced clinic visit with the remote one (phone call) or skipped at all the visit, spirometry and questionnaires data were not available at the missing clinic visit. As reported in section 7.3, missing data for variable repeatedly measured over time will be handled by MMRM model. It can be expected that in the phase "during COVID-19" a part of the visits could have missing data for spirometry and questionnaires.
- minor impact is expected on rescue medication endpoints. This information was recorded on paper diary by the patients at home regardless of the study period. As study medication, the rescue medication and paper diary during the COVID-19 pandemic was delivered at patient home if needed and in case of visits performed remotely, investigators were instructed to remind the patient to take correctly the study medication/rescue medication/concomitant medication and to continue to record data in the paper diary.
- There is no reason to expect any worsening in patient safety.

Sensitivity analysis will consist in performing the same statistical model (MMRM) planned for primary efficacy variable by adding the "COVID-19" factor at patient level by using the Flag:

- "N" = "study participation completed before 31st January 2020" included,
- "Y" = "study participation completed after 31st January 2020".

Subgroup Analysis will consist in performing, within groups of patients COVID-19 = "Y" and COVID-19 = "N", the same statistical model (MMRM) planned for the primary efficacy variable. Treatment effect will be estimated within each group of COVID-19.

8 Study Population

8.1 Disposition of Patients and Discontinuations

8.1.1 Disposition of Patients

The number of patients screened, the number of screen failures and the number of patients with each reason for screen failure will be presented overall. These summaries will be based on the Enrolled Set.

The number of patients randomised at Visit 2, who attended Visits 3, 4 and 5, who completed Visit 6, who discontinued and performed Early Termination visit and with follow-up contact available will be presented by treatment group and overall using the Randomised set.

The number of patients screened, randomised and completed will also be presented by region and site.

8.1.2 Discontinuation from the Study

The number and percentage of patients who completed the study, withdrew from the study after randomisation and the number and percentage of patients with each reason for discontinuation from the study will be presented by treatment group and overall using the Randomised set.

Time to discontinuation from the study after randomisation will be analysed using the Kaplan-Meier method for the Randomised set.

Time to discontinuation from the study (weeks) will be calculated as: (date of completion/discontinuation – date of start of randomised treatment period+1)/7. For patients randomised, but not treated, time to discontinuation from study will be assumed = 0.

In the Kaplan-Meier analysis of time to discontinuation, patients who complete the study will be censored at the date of completion.

For the study periods:

- [0-4) weeks;
- [4-12) weeks;
- [12-18) weeks;
- [18-24) weeks;
- [24 weeks-End of Study].

the number of patients in study at the beginning of the period, the cumulative number of discontinued patients at the end of the period and the probability of discontinuation at the end of the period with the associated 95% CIs will be presented by treatment group. Comparisons between treatments will also be performed by means of the log-rank test.

Figure of the time to discontinuation from the study by treatment group will also be presented.

8.1.3 Protocol Deviations and Analysis Sets

Major and minor protocol deviations will be summarised by treatment group and overall using the ITT set. Local major deviations will be presented in the listings only.

The number of patients included in each of the Randomised, Safety, ITT and PP sets will be summarised for each treatment group and overall. The summary will also be presented by region and site.

8.2 Demographic and Baseline Characteristics

No formal comparison between treatment groups on demographic and baseline characteristics will be performed.

For the final analysis, if the Safety and ITT sets are equal, the tables on the ITT set will not be presented if available also on the Safety Set.

8.2.1 Demographic Characteristics

Demographic characteristics will be summarised by treatment group and overall. This will include age, gender, race, height, weight and Body Mass Index (BMI). Separate summaries will be produced using the Randomised, Safety, ITT and PP sets.

Notes:

- height and weight recorded at Visit 1 will be presented;
- BMI will be calculated as: weight (kg) / height $(m)^2$.

8.2.2 COVID-19

The COVID-19 variable will be created according to the definition given in section 7.13.1. This variable will be summarised by means of descriptive statistics by randomised group and overall and will be included in the table of the demographic characteristics.
The variable will also be listed in the listings of demography.

8.2.3 Smoking status

Smoking status at screening (ex-smoker or current smoker), duration of smoking (years) and number of pack-years recorded at Visit 1 will be presented by treatment group and overall. Changes in smoking habits during the study (any change and distinguishing patients who started and patients who stopped smoking) will also be summarised. Separate summaries will be produced using the Safety, ITT and PP Sets.

Notes:

- for ex-smokers, duration of smoking (years) will be calculated as (stop date – start date + 1)/365.25;
- for current smokers, duration of smoking (years) will be calculated as (date of Visit 1 – start date + 1)/365.25.

8.2.4 COPD History

Time since first COPD diagnosis (years), COPD medication category at study entry (ICS/LABA, ICS/LAMA, LABA/LAMA, LAMA, LABA), number of COPD exacerbations in the previous year (as a continuous and categorical variable [1, >1 and also 1, 2, 3, >3]), time since last COPD exacerbation (months), treatment for the last COPD exacerbation (systemic corticosteroids only, antibiotics only, systemic corticosteroids and antibiotics, no systemic corticosteroids / no antibiotics), hospitalisation/emergency room for the last COPD exacerbation will be presented by treatment group and overall. Separate summaries will be produced using the Safety, ITT and PP sets.

Notes:

- Time since first COPD diagnosis (years) will be calculated as (date of Visit 1 – date of first COPD diagnosis)/365.25;
- Time since last COPD exacerbation (months) will be calculated as (date of Visit 1 – date of last COPD exacerbation)/30.4375.

8.2.5 Spirometry at Visit 1 and at Visit 2

The following spirometry parameters will be summarised by treatment group and overall:

- Visit 1: FEV_1, FVC, FEV_1/FVC, MMEF and IC pre-salbutamol intake; FEV_1, FEV_1 % of predicted normal value [as a continuous and categorical variable (<30%, ≥30%)], FVC, FEV_1/FVC and MMEF post-salbutamol intake.

- Visit 2: FEV_1, FVC, MMEF and IC pre-dose.

Separate summaries will be produced using the Safety, ITT and PP sets.

8.2.6 CAT and SGRQ at Visit 1 and Visit 2

The CAT total score at Visit 1 and Visit 2 and the SGRQ total score and domain scores at Visit 2 will be summarised by treatment group and overall using the ITT set.

8.2.7 Rescue Medication Use during the Run-in Period

The percentage of days without intake of rescue medication and the average use of rescue medication (number of puffs/day) during the run-in period will be summarised by treatment group and overall using the ITT set.

8.2.8 12-lead ECG at Visit 1

The number and percentage of patients with a pacemaker inserted before study entry and inserted during study and with atrial fibrillation will be presented. A patient will be classed as having a pacemaker or with atrial fibrillation according to the rule defined in section 7.10.1.4.

The average HR, QTcF, PR and QRS obtained in the triplicate 12-lead ECG at Visit 1 will be summarised by means of descriptive statistics by treatment group and overall using the Safety set.

8.2.9 Vital Signs at Visit 1 and Visit 2

SBP and DBP assessed at Visit 1 and Visit 2 (pre-dose) will be summarised by means of descriptive statistics by treatment group and overall using the Safety set. Pulse rate will be presented in the listings only.

8.3 Medical History and Concomitant Diseases

Medical/surgical history and concomitant diseases will be summarised by System Organ Class (SOC) and Preferred Term (PT), by treatment group and overall. Separate summaries will be produced using the Safety set.

Notes:

- Medical/surgical histories are defined as records in the medical/surgical history and concomitant diseases eCRF form which are not ongoing at Visit 1;
- Concomitant diseases are defined as records in the medical/surgical history and concomitant diseases eCRF form which are ongoing at Visit 1.

8.4 Medications

Previous medications, medications maintained during the randomised treatment period and concomitant medications will be summarised by treatment group and overall (except for concomitant medications) for the ITT set through frequency distributions and percentages by Anatomical Main Group [1st level of the Anatomical Therapeutic Chemical (ATC) classification], Therapeutic Subgroup (2nd level of the ATC classification), Chemical Subgroup (4th level of the ATC classification) and Preferred Name. Post-treatment medications will only be presented in a listing.

The medications will be classified according to the following rules:

- previous medication: stop date < date of start of randomised treatment period;
- medication maintained during the randomised treatment period: start date < date of start of randomised treatment period and stop date ≥ date of start of randomised treatment period or ongoing;
- concomitant medication: date of start of randomised treatment period ≤ start date ≤ date of end of randomised treatment period;
- post-treatment medication: start date > date of end of randomised treatment period.

In case of missing or incomplete dates not directly allowing allocation to any of the four categories of medications, see the rules defined in section 7.3.
If a patient has multiple occurrences of a medication, the patient is presented only once in the respective patient count.

In the analyses, some Preferred Names will be presented under a common name in order to improve the readability of the tables. The common name will be presented instead of the associated preferred names in the tables and the frequency distribution will be evaluated considering the common names (e.g., if one patient took two medications with different Preferred Names but the same common name, he/she will be counted only once under the common name in the tables). In the listing, the Preferred Names will not be replaced by the common names.

The following tables will be provided:

- previous medications
- medications maintained during the randomised treatment period
- concomitant medications.

Each table will be presented separately for COPD medications and non-COPD medications.
Any medications with an indication equal to 'COPD' or 'COPD exacerbation during the study' will be considered as COPD medications. A full review of the medications to identify medication taken for COPD will be performed during the DRM.

8.5 Procedures

Previous procedures, procedures maintained during the randomised treatment period and concomitant procedures will be summarised by treatment group and overall for the Safety set through frequency distributions and percentages by SOC and PT. Post-treatment procedures will only be presented in a listing.

The procedures will be classified according to the following rules:

- previous procedures: end date < date of start of randomised treatment period;
- procedures maintained during the randomised treatment period: start date < date of start of randomised treatment period and end date ≥ date of start of randomised treatment period or ongoing;
- concomitant procedures: date of start of randomised treatment period ≤ start date ≤ date of end of randomised treatment period;
- post-treatment procedures: start date > date of end of randomised treatment period.

8.6 Compliance

8.6.1 Treatment Compliance

In general, treatment compliance will be evaluated based on the information recorded daily by the patient on the diary. If for a dosing occasion both diary and eCRF data is available (e.g., for the morning dose on the days of the clinic visits), the eCRF data will be considered.

8.6.1.1 Run-in Period

Treatment exposure (days) is calculated as: date of last run-in study medication intake – date of first run-in study medication intake +1.

The date of first and last run-in study medication intake will be derived on the bases of the information recorded on the diary and the eCRF.

The evaluation of the compliance will be based on the following formula:

Compliance (%) = (# administered inhalations / # scheduled inhalations)*100.

The number of administered inhalations is equal to the sum of all inhalations taken during the run-in period (see Section 7.10.1.3). The number of administered inhalations will be taken from the diary and the eCRF (for inhalations administered at the site during the visits), assuming no intake of study medication on a morning/evening, if the relevant diary or eCRF data is missing.

The total number of scheduled inhalations will be calculated based on the following formula:

- # scheduled inhalations = (date of start of randomised treatment period - date of Visit 1) (days) * 4 (2 inhalations b.i.d.).

Descriptive summaries of treatment compliance (%) will be presented by treatment group for the run-in period using the ITT set. An additional summary displaying the number and percentage of patients in the following categories will also be presented by treatment group:

- [0%-50%)
- [50%-75%)
- [75-100%)
- [100%-125%]
- >125%

8.6.1.2 Randomised Treatment Period

Treatment exposure (days) is calculated as: date of last randomised study medication intake - date of first randomised study medication intake + 1.

The date of first and last randomised study medication intake are defined in section 7.8.2.

The evaluation of the compliance will be based on the following formula:

Compliance (%) = (# administered inhalations / # scheduled inhalations)*100.

The number of administered inhalations will be calculated as the total number of inhalations taken from the evening session of the day of first randomised study medication intake to the day of last randomised study medication intake, inclusive. It will be taken from the diary and

the eCRF (for inhalations administered at the site during the visits), assuming no intake of study medication on a morning/evening, if the relevant diary or eCRF data is missing.

The total number of scheduled inhalations will be calculated on the basis of the extent (days) of exposure of each patient. The evaluation of the total number of scheduled inhalations will be based on the following formula:

- # scheduled inhalations = Extent of exposure (days) * 8 (4 inhalations b.i.d.).

If the last day of exposure is the date of Visit 6 (date of last randomised study medication intake = Date of Visit 6), the number of scheduled inhalations on this day will be 4 (4 inhalations) as study medications will be administered only in the morning. Therefore, the total number of scheduled inhalations will be:

- (Date of last randomised study medication intake - Date of first randomised study medication intake) * 8 + 4.

For patients with date of discontinuation = date of Visit 2, then:

- # scheduled inhalations = 4 (2 inhalations of CHF 1535 100/6 µg pMDI active or placebo + 2 inhalations of Symbicort® Turbohaler® 160/4.5 µg active or placebo).

A range of 75-125% will be considered for a satisfactory level of compliance.
Descriptive summaries of treatment compliance (%) will be presented by treatment group for the randomised treatment period using the ITT set. An additional summary displaying the number and percentage of patients in the following categories will also be presented by treatment group:

- [0%-50%)
- [50%-75%)
- [75-100%)
- [100%-125%]
- >125%

8.6.2 Diary Compliance

Diary compliance will be summarised on the ITT set.

8.6.2.1 Run-in Period

Sessions recorded from the evening of the day of the Visit 1 to the morning of the day of start of randomised treatment period will be considered as data of the run-in period.

A morning/evening session is considered "with data recorded in the diaries" if at least one of the following fields has been filled-up: number of run-in medication puffs in the morning/evening, number of rescue medication puffs in the morning/evening.

Compliance to the use of diaries during the run-in period will be calculated according to the number of sessions using the following formula:

- Compliance during the run-in period (%) = [Total number of sessions in the run-in period with data recorded in the diaries / ((Date of start of randomised treatment period – Date of Visit 1)*2)]*100.

Compliance to the use of diaries during the run-in period will be summarised by treatment group by means of descriptive statistics. The number and the percentage of patients in the following categories of compliance will also be presented:

- [0%-50%)
- [50%-60%)
- [60%-70%)
- [70%-80%)
- [80%-90%)
- [90%-100%].

8.6.2.2 Randomised Treatment Period

Sessions recorded from the evening of the day of start of randomised treatment period to the day of end of randomised treatment period will be considered as data of the randomised treatment period.

A morning/evening session is considered "with data recorded in the diaries" when at least one of the following fields has been filled-up: number of study medications puffs (pMDI and/or Symbicort Turbohaler) in the morning/evening, number of rescue medication puffs in the morning/evening.

If the day of end of randomised treatment period is the day of a clinic visit, the following formula will be used:

- Compliance during the randomised treatment period (%) = [Total number of sessions in the randomised treatment period with data recorded in the diaries / (2*(Date of end of randomised treatment period – Date of start of randomised treatment period))]*100.

Otherwise, the following formula will be used:

- Compliance during the randomised treatment period (%) = [Total number of sessions in the randomised treatment period with data recorded in the diaries / (2*(Date of end of randomised treatment period – Date of start of randomised treatment period) + 1)]*100.

Compliance to the use of diaries during the randomised treatment period will be summarised by treatment group by means of descriptive statistics. The number and the percentage of patients will also be presented in the same categories of compliance above defined for the run-in period.

9 Efficacy Analyses

Summary and analysis on the primary efficacy variable will be performed on ITT and PP sets. Since the study is based on a non-inferiority hypothesis, for the primary efficacy analysis the ITT and the PP sets will have equal importance.
Sensitivity and subgroup analysis on the primary efficacy variable will be performed on ITT set. Summaries and analyses on each secondary efficacy variable will be performed on ITT set.

9.1 Primary Efficacy Variable

9.1.1 Change from baseline in pre-dose morning FEV_1 at Week 24 (Visit 6)

Since the analysis of change from baseline in pre-dose morning FEV_1 at Week 24 is based on the same statistical model used for the analysis of change from baseline in pre-dose morning

FEV_1 at all the other clinic visits, details on these secondary efficacy variables are also provided in this section.

Baseline is the pre-dose morning FEV_1 recorded at Visit 2.

Pre-dose morning FEV_1 values at each visit will be summarised by treatment group using descriptive statistics. Change from baseline at each visit will also be summarised by treatment group.

Change from baseline in pre-dose morning FEV_1 will be analysed using a linear MMRM including treatment, visit, treatment by visit interaction, region, number of COPD exacerbations in the previous year (1, >1), severity of airflow limitation at screening (post-bronchodilator FEV_1 % predicted <30%, ≥30%) and smoking status at screening (ex-smoker, current smoker) as fixed effects, and baseline value and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed and the Kenward-Roger adjustment will be used for the degrees of freedom. The number of patients considered in the model will be provided by treatment group. P-values of the effects will also be presented.

The adjusted means in each treatment group, the adjusted mean differences between treatments, their 95% CIs and associated p-values at each visit will be estimated by the model.

Non-inferiority of CHF 1535 pMDI over Symbicort® Turbohaler® will be demonstrated if the lower confidence limit of the 95% CI of the adjusted mean difference between CHF 1535 100/6 µg pMDI and Symbicort® Turbohaler® at Week 24 will be > -0.07L. In addition, the non-inferiority p-value will be reported.

The above comparison between treatments at all the other visits will also be presented.

The same descriptive and statistical analyses will also be performed on PP set.

A figure with adjusted mean change from baseline at each visit by treatment group derived from the linear MMRM will also be provided on ITT and PP sets.

The analysis of pre-dose morning FEV_1 based on the linear MMRM will be also presented on the ITT set stratifying as detailed in Section 7.6 (note: also summary of pre-dose morning FEV_1 will be provided for this stratification).

The adjusted mean differences between treatments at Week 24 (Visit 6) and their 95% CIs estimated on the ITT and PP sets and in the stratified analyses will be graphically summarised in a forest plot (this means a total of one forest plot only).

9.1.1.1 Sensitivity and Subgroup analysis to investigate the impact of COVID-19

The same descriptive statistics reported in section 9.1.1 will be summarised for subgroups of patients based on COVID-19 variable ("Y", "N").

The same MMRM model reported in section 9.1.1 with the inclusion of the COVID-19 variable as fixed factor will be performed.

The same MMRM model reported in section 9.1.1 will also be performed on subgroups of patients based on COVID-19 variable ("Y", "N").

The descriptive statistics and statistical models will be performed on ITT set.

9.2 Secondary Efficacy Variables

The secondary efficacy variables will be analysed on the ITT set.

9.2.1 Change from baseline in pre-dose morning FEV_1 (L) at all the other clinic visits

Since the analysis of the primary efficacy variable (change from baseline in pre-dose morning FEV_1 at Week 24, Visit 6) is based on the same statistical model used for the analysis of change from baseline in pre-dose morning FEV_1 at Visits 3, 4, 5, 6, details on the analysis are provided in section 9.1.1.

9.2.2 FEV_1 Response at Week 24

Baseline is the pre-dose morning FEV_1 recorded at Visit 2.

FEV_1 response is defined as a change from baseline in pre-dose morning $FEV_1 \geq 100$ mL. If the change from baseline is < 100 mL the patient is classified as a non-responder in terms of FEV_1. Patients with missing change from baseline in pre-dose morning FEV_1 at Week 24 will also be classified as non-responders (whatever the reason of the missing change from baseline value, patient withdrawn and no data are reallocated at the visit, patient is present at the Visit but does not have a baseline value or does not have any value available at the visit).

The number and percentage of FEV_1 responders/non-responders (distinguishing also the two categories of non-responders: with a change from baseline actually < 100 mL or with missing data) at Visit 6 will be presented by treatment group.

FEV_1 response at Week 24 will be compared between treatment groups using a logistic model including treatment, region, number of COPD exacerbations in the previous year (1 or >1), severity of airflow limitation at screening (post-bronchodilator FEV_1 % predicted <30%, ≥30%) and smoking status at screening (ex-smoker, current smoker) as factors and the baseline FEV_1 value as a covariate.

The number of patients considered in the model will be provided by treatment group. P-values of the effects based on Wald chi-square test will also be presented.

The odds ratio for the treatment effect (CHF 1535 pMDI vs. Symbicort® Turbohaler®) with its 95% Wald CI and corresponding p-value will be estimated by the model.

9.2.3 Change from baseline in pre-dose morning FVC (L) at all clinic visits

Baseline is the pre-dose morning FVC recorded at Visit 2.

Pre-dose morning FVC values will be summarised at each visit by treatment group using descriptive statistics. Change from baseline will also be summarised at each post-baseline visit by treatment group.

Change from baseline in pre-dose morning FVC values at Visits 3, 4, 5, 6 will be analysed using the same model as change from baseline in pre-dose morning FEV_1 (see section 9.1.1). Baseline FVC will be included as a covariate rather than baseline FEV_1.

9.2.4 Change from baseline in pre-dose morning IC (L) at all clinic visits

Baseline is the pre-dose morning IC recorded at Visit 2.

Pre-dose morning IC values will be summarised at each visit by treatment group using descriptive statistics. Change from baseline will also be summarised at each post-baseline visit by treatment group.

Change from baseline in pre-dose morning IC values at Visits 3, 4, 5, 6 will be analysed using the same model as change from baseline in pre-dose morning FEV_1 (see section 9.1.1). Baseline IC will be included as a covariate rather than baseline FEV_1.

9.2.5 Change from baseline in pre-dose morning MMEF at all clinic visits

Baseline is the pre-dose morning MMEF recorded at Visit 2.

Pre-dose morning MMEF values will be summarised at each visit by treatment group using descriptive statistics. Change from baseline will also be summarised at each post-baseline visit by treatment group.

Change from baseline in pre-dose morning MMEF values at Visits 3, 4, 5, 6 will be analysed using the same model as change from baseline in pre-dose morning FEV_1 (see section 9.1.1). Baseline MMEF will be included as a covariate rather than baseline FEV_1.

9.2.6 Change from baseline in the SGRQ Total Score and Domain Scores at all clinic visits

Baseline is the SGRQ total and domain scores recorded at Visit 2.

For the SGRQ, the following scores will be calculated:

- Symptoms score: sum of weights of positive items to questions 1 to 8 of Part 1. Only one item should be ticked. In case more than one item is ticked for one question from 1 to 7, the mean of weights of positive items will be considered for that question;
- Impacts score: as sum of weights of positive items to sections 1, 3, 4, 5 and 7 of Part 2. For questions of section 1 only one item should be ticked. In case more than one item is ticked for one question, the mean of weights of positive items will be considered for that question;
- Activity score: sum of weights of positive items to sections 2 and 6 of Part 2;
- Total score: it will be calculated as sum of all positive items of questionnaire. The same rules above defined in case of multiple responses apply.

Each domain will be calculated as follows:

- Score = (sum of the weights of the positive items of that domain / sum of the weights of all items of that domain)*100.

The total score will be calculated as follows:

- Score = (sum of the weights of the positive items of all domains / sum of the weights of all items of all domains)*100.

Missing data will be dealt with as described in Section 7.3.

SGRQ total and domain (symptoms, impacts and activity) scores will be summarised at each visit by treatment group using descriptive statistics. Changes from baseline will also be summarised at each post-baseline visit by treatment group.

Change from baseline in SGRQ total and domain (symptoms, impacts and activity) scores at Visits 4 and 6 will be analysed using the same model as for change from baseline in pre-dose morning FEV_1 (see section 9.1.1). Baseline total/domain scores will be included as a covariate rather than baseline FEV_1.

9.2.7 Change from baseline in COPD Assessment Test (CAT) at all clinic visits

Baseline is the CAT score recorded at Visit 2.

CAT total score will be summarised at each visit by treatment group using descriptive statistics. Changes from baseline will also be summarised at each post-baseline visit by treatment group.

Change from baseline in CAT total score at Visits 3, 4, 5, 6 will be analysed using the same model as for change from baseline in pre-dose morning FEV_1 (see section 9.1.1). Baseline CAT total score will be included as a covariate rather than baseline FEV_1.

9.2.8 Change from baseline to each inter-visit treatment period and to the entire treatment period in percentage of days without intake of rescue medication

The following algorithms should be considered for the percentage of rescue medication-free days:

Variable	Definition
Daily use of rescue medication	Daily use of rescue medication will be calculated based on data recorded daily by the patient on the diaries. A day will be constituted by the data recorded in the evening session of that day plus the data recorded in the morning session of the next day. For each day, the "daily use of rescue medication" will be calculated as the sum of the number of puffs taken during the day (i.e., recorded in the evening session of that day) and taken during the night (recorded in the morning session of the next day). For each day, the daily use of rescue medication will be calculated only if data at both evening and morning sessions are available.
Rescue medication-free days	A rescue medication-free day is a day with daily use of rescue medication = 0.
Baseline percentage of rescue medication-free days	100*(no. of rescue medication-free days during baseline period / no. of days with available daily use of rescue medication during baseline period) with number of rescue medication-free days during baseline period and number of days with available daily use of rescue medication during baseline period calculated considering data recorded in the entire run-in period. Data on rescue medication use recorded in the morning session of the date of start of randomised treatment period will be considered as a measurement of the baseline period.
Percentage of rescue medication-free days at each inter-visit period	100*(number of rescue medication-free days during the inter-visit period / number of days with available daily use of rescue medication during the inter-visit period) with number of rescue medication-free days during the inter-visit period and number of days with available daily use of rescue medication during the inter-visit period calculated on the data recorded from the evening session of the day of clinic visit to the morning session of the day of next clinic visit (or date of end of randomised treatment period for last inter-visit period). For the period Visit 2 – Visit 3 (first inter-visit period), the date of start of randomised treatment period will be considered as reference point instead of date of Visit 2.

Percentage of rescue medication-free days over entire treatment period	100*(number of rescue medication-free days over entire treatment period / number of days with available daily use of rescue medication over entire treatment period) with number of rescue medication-free days over entire treatment period and number of days with available daily use of rescue medication over entire treatment period calculated on the data recorded from the evening session of the date of start of randomised treatment period to the morning session of the date of end of randomised treatment period.

Percentage of rescue medication-free days at baseline, at each inter-visit period and over the entire treatment period will be summarised by treatment group using descriptive statistics. Change from baseline in percentage of rescue medication-free days at each inter-visit period and over the entire treatment period will also be summarised by treatment group.
Change from baseline to each inter-visit treatment period in percentage of rescue medication-free days will be analysed using a linear MMRM with change from baseline to each inter-visit period as dependent variable, with treatment, inter-visit period, treatment by inter-visit period interaction, region, number of COPD exacerbation in the previous year (1 vs. >1), severity of airflow limitation at screening (post-bronchodilator FEV_1 % predicted <30%, ≥30%) and smoking status at screening (ex-smoker, current smoker) as fixed effects, and baseline value and baseline by inter-visit period interaction as covariates. An unstructured covariance matrix will be assumed and the Kenward-Roger adjustment will be used for the degrees of freedom.

The number of patients considered in the model will be provided by treatment group. P-values of the effects will also be presented.

The adjusted means in each treatment group, the adjusted mean differences between treatments, their 95% CIs and associated p-values at each inter-visit period and over the entire treatment period will be derived by the model.

A figure with adjusted mean change from baseline to each inter-visit period by treatment group derived from the linear MMRM will also be provided.

9.2.9 Change from baseline to each inter-visit treatment period and to the entire treatment period in average use of rescue medication (number of puffs/day)

The following algorithms should be considered for the use of rescue medication:

Variable	Definition
Baseline average use of rescue medication	The mean of all daily use of rescue medication (see section 9.2.8 for definition) recorded during the entire run-in period. Data on rescue medication use recorded in the morning session of the date of start of randomised treatment period will be considered as a measurement of the baseline period.

Variable	Definition
Average use of rescue medication at each inter-visit period	The mean of all daily use of rescue medication values recorded from the evening session of the day of clinic visit to the morning session of the day of next clinic visit (or date of end of randomised treatment period for last inter-visit period). Data of rescue medications recorded in the morning session of the day of each clinic visit will be considered as a measurement of the inter-visit period before that clinic visit. For the period Visit 2 – Visit 3 (first inter-visit period), the date of start of randomised treatment period will be considered as reference point instead of date of Visit 2.
Average use of rescue medication over entire treatment period	The mean of all daily use of rescue medication values from the evening session of the date of start of randomised treatment period to the morning session of the date of end of randomised treatment period.

Change from baseline to each inter-visit treatment period and over the entire treatment period in average use of rescue medication will be analysed using the same descriptive statistics and the same statistical models provided for the percentage of rescue medication-free days.

A figure with adjusted mean change from baseline to each inter-visit period by treatment group derived from the linear MMRM will also be provided.

9.2.10 Rate of Moderate and Severe COPD Exacerbations over 24 Weeks of Treatment

Moderate and Severe COPD exacerbations during the randomised treatment period derived from the COPD exacerbations eCRF form will be considered for the analysis.

Only COPD exacerbations with date of start of randomised treatment period ≤ start date ≤ date of end of randomised treatment period will be considered in the analysis.

Two COPD exacerbations will be considered as a single episode in the statistical analysis if the second exacerbation started less than 10 days after the end of the systemic corticosteroids and/or antibiotics intake for the previous exacerbation (start date of the following exacerbation - end date of the treatment of the previous exacerbation < 10 days) or if the second exacerbation started less than 10 days after the onset of the previous exacerbation (start date of the following exacerbation – onset date of an exacerbation < 10 days).

In case of more than two exacerbations on the same patient, this rule will be applied iteratively (therefore more than two exacerbations may be considered as a single episode). This rule will not be applied for the analysis of COPD exacerbations as AEs.

In case of COPD exacerbations considered as a single episode:

- the start date of the first event will be considered as the start date;
- the stop of the last event will be considered as the stop date;
- a worst-case approach will be considered for the following characteristics of the exacerbation: severity of exacerbation (for example if one of two exacerbations considered as a single episode was moderate and the other one was severe, the single episode will be considered in the analysis as a severe exacerbation), exacerbation leading to death, requirement of hospitalisation (taking into account that emergency room admissions with more than 24 hours of stay should also be considered as hospitalisations, see the paragraph below), requirement of emergency visit;

- the treatment will be defined considering the treatments of all the exacerbations to be considered as a single episode (for example if one of the exacerbations was treated using systemic corticosteroids only and another one using antibiotics only, the resulting event will be considered as treated with systemic corticosteroids and antibiotics);
- if the etiologies of the exacerbations to be considered as a single episode are different, the resulting single event will be considered as having multiple etiology (for example if one of two exacerbations considered as a single episode has etiology "*Viral or bacterial*" and the other one has etiology "*Concomitant Pulmonary Diseases*", the single episode will be considered in the analysis as having multiple etiology "*Viral or bacterial*" and "*Concomitant Pulmonary Diseases*"). It should be noted that it is already possible for the Investigator to record multiple etiology for each COPD exacerbation. If the etiology is non-missing for at least one of the exacerbations to be considered as a single episode, the resulting single event will be counted only under the non-missing etiology and not under the "*Missing*" category.

Emergency room admissions with more than 24 hours of stay (date/time of discharge – date/time of admission > 24 hours) will be also considered as hospitalisations in the statistical analysis.

A COPD exacerbation will be classified as severe if at least one of the following conditions is satisfied:

- it required hospitalisation ("*Hospitalisation"* = Yes in the COPD exacerbation form of the eCRF);
- it required emergency room admission ("*Emergency Room*" = Yes in the COPD exacerbation form of the eCRF) with more than 24 hours of stay (event to be considered as a hospitalisation), irrespective whether associated or not with systemic corticosteroids or antibiotics;
- it resulted in death (outcome = "*Fatal*" in the AE / COPD exacerbation form of the eCRF).

A COPD exacerbation which required emergency room admission ("*Emergency Room*" = Yes in the COPD exacerbation form of the eCRF) with less than or equal to 24 hours of stay and associated with systemic corticosteroids and/or antibiotics, will be classified as moderate COPD exacerbation.

The number and the percentage of patients with moderate/severe COPD exacerbations, the number of moderate/severe COPD exacerbations and the total follow-up time in years will be summarised by treatment group.

The follow-up time in years will be calculated using the following formula:

- Follow-up time (years) = (date of end of randomised treatment period - date of start of randomised treatment period + 1) / 365.25.

The rate of moderate/severe COPD exacerbations per patient per year will be calculated for each treatment using a weighted approach (which consists of pooling all patients of a treatment group and dividing the total number of COPD exacerbations by the total follow-up time).

The number and the percentage of patients with exacerbations, the number of exacerbations and the exacerbation rate per patient per year will also be presented by treatment group for each of the following types of exacerbation:

- Moderate COPD exacerbations;
- Severe COPD exacerbations;
- COPD exacerbations leading to death;
- COPD exacerbations requiring hospitalisation.

The number and the percentage of exacerbations treated with systemic corticosteroids and antibiotics, with systemic corticosteroids only and with antibiotics only will be also presented by treatment group.

A COPD exacerbation will be defined as treated with systemic corticosteroids if this treatment is recorded in the COPD exacerbation form of the eCRF. A COPD exacerbation will be defined as treated with antibiotics if this treatment is recorded in the COPD exacerbation form of the eCRF.

In case of hospitalisation for COPD exacerbation, the duration of hospitalisation (days) will be calculated using the following formula:

- date of discharge – date of admission + 1.

The number of moderate and severe COPD exacerbations during the treatment period will be analysed using a negative binomial model including treatment, region, number of COPD exacerbations in the previous year (1 or >1), severity of airflow limitation at screening (post-bronchodilator FEV_1 % predicted <30%, ≥30%) and smoking status at screening (ex-smoker, current smoker) as fixed effects, and log-time on study in years as an offset. The adjusted exacerbation rates in each treatment group and the adjusted rate ratio with their 95% Wald CIs will be estimated by the model.

The number of patients considered in the model will be provided by treatment group. P-values of the effects based on Wald chi-square test will also be presented.

The log-time on study in years will be calculated using the following formula:

- Log-time on study = ln(Follow-up time).

Individual rate of COPD exacerbations will be calculated for each patient using the following formula:

- Individual rate = number of COPD exacerbations / follow-up time (years).

Individual rates will be listed only.

9.2.11 Time to First Moderate / Severe COPD Exacerbation

In patients with at least one moderate/severe COPD exacerbation, time to first moderate/severe COPD exacerbation will be calculated as the time in weeks between the start date of randomised treatment period and the date at which the first COPD exacerbation occurs.

- Time to first moderate/severe COPD exacerbation (weeks) = (date of start of first moderate/severe COPD exacerbation – date of start of randomised treatment period+1)/7.

Patients without a moderate/severe COPD exacerbation or who are discontinued before having it will be considered as "censored" at date of end of randomised treatment period. For the analysis, the following formula will be applied:

- Censoring time (weeks) = (date of end of randomised treatment period – date of start of randomised treatment period +1)/7

The number of moderate/severe COPD exacerbation-free patients at the beginning of the period, the cumulative number of patients with moderate/severe COPD exacerbation at the end of the period and the probability of having experienced a moderate/severe COPD at the end of the period with the associate 95% CIs will be presented by treatment group for the following study periods:

- [0-4) weeks;
- [4-12) weeks;
- [12-18) weeks;
- [18-24) weeks;
- [24 weeks-EoT];

using Kaplan-Meier analysis. The point estimates and the relative 95% CIs will be presented by treatment group for the 75th, 50th and 25th percentiles.

A Kaplan-Meier plot will also be presented.

The time to first moderate/severe COPD exacerbation will be analysed using a Cox proportional hazards model including treatment, region, number of COPD exacerbations in the previous year (1 or >1), severity of airflow limitation at screening (post-bronchodilator FEV_1 % predicted <30%, ≥30%) and smoking status at screening (ex-smoker, current smoker) as factors.

The number of patients considered in the model will be provided by treatment group. P-values of the effects based on Wald chi-square test will also be presented.

The treatment effect (CHF 1535 pMDI vs. Symbicort® Turbohaler®) will be presented as a hazard ratio with the associated 95% Wald CI and p-value.

10 Safety Analyses

All analyses of safety variables will be performed on the Safety set.

10.1 Extent of Exposure

The extent of exposure (days) will be calculated using the following formula:

- Extent of exposure (days) = Date of last randomised study medication intake - Date of first randomised study medication intake +1.

The extent of exposure will also be calculated in weeks using the following formula:

- Extent of exposure (weeks) = Extent of exposure (days) / 7.

The number and the percentage of patients with the following 4-week categories of extent of exposure will also be presented:

- [0-4]
- (4-12]
- (12-18]
- (18-24]
- >24

Descriptive statistics of extent of exposure in days and weeks will be provided by treatment group.

10.2 Adverse Events

Data on COPD exacerbation as adverse event will be reported in a dedicated eCRF form "*Assessment of COPD exacerbation as Adverse Event"*. Therefore, COPD exacerbations can also be analysed as AEs and included in the analysis of AEs (tables and listings).

The AEs will be classified according to the following rules:

- Pre-treatment AE: AE onset date < date of first randomised study medication intake.
- TEAE: date of first randomised study medication intake ≤ AE onset date ≤ date of last randomised study medication intake.
- Post-treatment AE: AE onset date > date of last randomised study medication intake.

An ADR is an AE classified as related to the study medication.

A serious ADR is a serious AE (SAE) classified as related to the study medication.

A severe AE is an AE with severe intensity.

An AE leading to study medication discontinuation is an AE with action taken with study drug equal to "*Drug Withdrawn*".

An AE leading to death is an AE with outcome equal to "*Fatal*".

Two AEs with the same PT and classified in the same category (pre-Treatment AE, TEAE or post-treatment AE) will be considered as two different events when calculating the "number of events" in the tables.

The relative day of AE onset will be calculated as follows:

- For pre-Treatment AEs: AE onset date - date of first randomised study medication intake;
- For TEAEs: AE onset date - date of first randomised study medication intake +1;
- For post-treatment AEs: AE onset date - date of last randomised study medication intake.

Relative day will not be calculated if AE onset date is incomplete or unknown.

The duration of an AE will be calculated as follows:

- AE end date – AE onset date + 1 (when both dates are completely known and AE is resolved);
- Date of completion/discontinuation – AE onset date + 1 (when the AE onset date is fully known but the AE is not resolved at the end of the trial): in this case the duration will be presented as ">x days" in the listing rather than "x days";

The AE duration will not be calculated if the AE onset date is incomplete or unknown, or if the AE was resolved but with an incomplete or unknown end date.

Pre-Treatment AEs, TEAEs and post-treatment AEs will be presented separately. Pre-Treatment AEs and post-treatment AEs will be presented in the listings only.

An overall summary of number and percentage of patients with at least one treatment-emergent AEs, SAEs, non-SAEs, ADRs, serious ADRs, severe AEs, AEs leading to study

medication discontinuation and AEs leading to death will be presented by treatment. The number of events will also be displayed.

The number and percentage of patients with at least one AE and the number of AEs will be presented by treatment group for treatment-emergent AEs, SAEs, non-SAEs, ADRs, serious ADRs, severe AEs, AEs leading to study medication discontinuation and AEs leading to death. Tables will be presented by SOC and then by PT, alphabetically sorted.

A table presenting the number and percentage of patients with at least one AE and the number of AEs for the most common TEAEs (reported in at least 3% of patients in any treatment group) will be provided. PTs only will be used for tabulation.

10.3 Vital Signs

Baseline is the vital signs value recorded at Visit 2.

Pre-dose vital signs (SBP and DBP) and their changes from baseline will be summarised by treatment group at each visit from Visit 2 onwards using descriptive statistics and the 95% CI of the mean.

Pulse rate will be presented in the listings only.

10.4 12-lead ECG

12-lead ECGs will be performed at Visit 1 and Visit 6 (Week 24/ETV).

Baseline is the 12-lead ECG parameters value recorded at Visit 1 (screening).

For 12-lead ECG parameters (average of the triplicate of HR, QTcF, PR and QRS), the absolute values and the changes from baseline will be summarised by treatment group using descriptive statistics. For the change from baseline, the 90% CI of the mean will also be provided.

The number and the percentage of patients with:

- For males:
  - QTcF > 450 ms and <= 480 ms
  - QTcF > 480 ms and <= 500 ms
  - QTcF > 500 ms
- For females:
  - QTcF > 470 ms and <= 500 ms
  - QTcF > 500 ms
- change from baseline in QTcF
  - >30 ms and <= 60 ms
  - >60 ms

at Visit 6 will be presented by treatment group. The percentages for this summary will be calculated on the number of patients with available data.

10.5 Laboratory findings

The laboratory parameters will be recorded at Visit 1 (screening) and Visit 6 (Week 24/ETV).

Laboratory parameter values reported as "< X" (i.e., below the lower limit of Quantification) or "> X" (i.e., above the upper limit of quantification) will be considered as "X" in the computations for quantitative summaries but will be presented in the listings as recorded (i.e., as "< X" or "> X").

Laboratory results at Visit 1 and Visit 6 and change from Visit 1 to Visit 6 will be summarised by treatment group (based on SI units). The 95% CI for the mean change will also be presented.

Shift tables from Visit 1 to Visit 6, with regard to normal range (low CS, low NCS, normal, high NCS, high CS), will be presented by treatment group for each laboratory parameter.

All laboratory data will be listed with abnormal values flagged. Pregnancy test results will be only listed.

11 Other Analyses

No other analyses planned.

12 Changes in the Planned Analyses from Study Protocol

- The severity of airflow limitation at screening, measured by FEV_1% predicted, is not included in the statistical models as fixed effect given the current CSP (refer to sections 12.3.4 and 12.3.5 of the CSP). However, the importance of the severity of airflow limitation at screening on the efficacy outcomes was revisited and, considering that the study was stratified by site only, the adjustment of the statistical models by including the severity of airflow limitation at screening as fixed effect is justified.
- In each statistical model the covariate "site" has been replaced by the covariate "region" according to the following categorization:

Region	Cities and provinces	Site number
North China	Beijing, Tianjin, Shanxi, part of inner Mongolia	15611, 15613, 15626, 15640, 15609, 15633, 15638, 15649, 15603
Northeast of China	Jilin, Liaoning	15643, 15658, 15648
East China	Shanghai, Jiangsu, Zhejiang, Anhui, Jiangxi, Shandong, Fujian	15601, 15606, 15610, 15625, 15628, 15629, 15631, 15621, 15627, 15632, 15657, 15602, 15642, 15604, 15635, 15639, 15659, 15644, 15636
Central China	Henan, Hunan	15617, 15654, 15622, 15647, 15651, 15653
South China	Guangdong, Guangxi, Hainan	15607, 15614, 15618, 15619, 15630, 15646, 15656, 15623, 15645
Western China	Chongqing, Sichuan, Guizhou, Gansu	15616, 15634, 15605, 15637, 15650

- FEV_1 response (change from baseline in pre-dose morning $FEV_1 \geq 100$ mL) has been added as secondary efficacy variable. As reported in Section 7.3, under the MAR assumption, the linear MMRM provides unbiased estimates of the treatment effect that would have been observed if all patients had continued on treatment for the full study duration. For this reason, these can be considered as robust estimates of the treatment effect. Usually other sensitivity analyses (copy reference / jump to

reference) are considered to strengthen the results derived under the MAR assumption. Unfortunately these methods (based on the data distribution of the reference group in both reference and active groups) can be applied only in superiority trials, since only in these context they provide conservative results (i.e.,: under the assumption that reference treatment provides worse result than the active). In a non-inferiority trial these methods are anti-conservative and cannot be applied. For this reason, in this trial no formal sensitivity analysis will be planned. Aiming at getting primary efficacy results more robust, a responder analysis has been added.

- A new variable COVID-19 has been created and stored in ADaM dataset to classify patients as "before" or "during" COVID-19 outbreak (section 7.13.1).
- Subgroups and sensitivity analysis to check the impact of COVID-19 on primary efficacy endpoint have been planned (section 9.1.1.1).
- For the daily variables recorded by the patients on the diary (average use of rescue medications, rescue-use free days), the availability of at least 14 measurements will be required during run-in period (as baseline) and at each inter-visit period. In the study protocol there was no requirement for these variables.
- Confidence interval for 12-leads ECG parameters (HR, QTcF, PR and QRS): change from baseline will be described with its 90% CI instead of the 95% CI (as reported in the study protocol).
- Abnormalities in ECG:
  Number and percentage of patients with QTcF absolute values (by gender):
  - QTcF >450 ms and <=480 ms, >480 ms and <= 500 ms, >500 ms for males and QTcF >470 ms and <= 500 ms, >500 ms for females;

  This criteria was reported in the study protocol as follows:
  - Number and percentage of patients with QTcF >450 ms, >480 ms and >500 ms.

  There was no differentiation between males and females, not taking into account of the exclusion criteria no. 12, which differentiates between genders.

13 Output

13.1 Software

All statistical analyses and data processing will be performed using Statistical Analysis Systems (SAS®) Software (release 9.4 or later).

13.2 Reporting Conventions

13.2.1 Treatment, Visit and Subgroup Descriptors

In the tables, listings and figures, the treatments and the visits will be identified as described below.

Treatment group	*Descriptor*
CHF 1535 100/6 µg pMDI	CHF 1535 pMDI
Symbicort® Turbohaler® 160/4.5 µg	Symbicort® Turbohaler®

Output	*Descriptor for visits*

Tables	Visit 1 (Week -4), Visit 1.1 (Week -1), Visit 2 (Week 0), Visit 3 (Week 4), …
Listings	Just the visit number (1, 1.1, 2, …) will be presented in the "Visit" column.
Figures	V1, V1.1, V2, V3, …

Subgroup	***Descriptor***
Severity of Airflow Limitation	Severity of Airflow Limitation: FEV1 % predicted <30%
	Severity of Airflow Limitation: FEV1 % predicted >=30%
Smoking Status at Screening	Smoking Status at Screening: Ex-Smoker
	Smoking Status at Screening: Current Smoker
Number of COPD exacerbations in the previous year	Number of COPD exacerbations in the previous year: 1
	Number of COPD exacerbations in the previous year: >1
COVID-19	Completed/discontinued before COVID-19 outbreak (≤31JAN2020)
	Completed/discontinued after COVID-19 outbreak (>31JAN2020)

13.2.2 Decimal places

Wherever possible, data will be decimal aligned.

Numeric variables will be listed with the same number of decimal places as in the actual data.

The following rules on decimal places will be considered in the listings for the derived variables (in the analyses rounding will not be performed):

- duration of hospitalisation for COPD exacerbations (days), duration of AE (days), relative day of AE, extent of exposure (days), average HR (beats/min), average QTcF (ms), average PR (ms), average QRS (ms), average SBP (mmHg), average DBP (mmHg): whole numbers;
- BMI (kg/m^2), time to discontinuation (weeks), time since first COPD diagnosis (years), time since last COPD exacerbation (months), duration of smoking (years), SGRQ scores, compliance, time to first COPD exacerbation (weeks), average use of rescue medication (daily mean number of puffs), percentage of rescue medication-free days, extent of exposure (weeks): 1 decimal place;
- change from baseline/screening: same as the variable considered.

The following rules on decimal places will be considered for the results of the analyses (if the analyses are performed on derived variables, the level of precision of the actual data is derived from the previous list):

- min, max: same as actual data;
- mean and its confidence limits (unadjusted and adjusted), SD, median: actual data + 1 decimal place;
- percentage: 1 decimal place;
- Kaplan-Meier percentiles estimates and confidence limits: actual data + 1 decimal place (3 decimal places for survival probabilities);
- hazard ratio and its confidence limits, odds ratio and its confidence limits: 3 decimal places;

The following rules on decimal places will be considered in the tables and listings for the analysis of COPD exacerbations:

- individual rate (per year): 1 decimal place;

- total follow-up time (years): 2 decimal places;
- individual follow-up time (years), rate (per patient per year, unadjusted and adjusted), confidence limits of adjusted rate ratio: 3 decimal places.

P-values, if applicable, will be presented to 3 decimal places. If the p-value is less than 0.001 then it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999.

13.2.3 Other reporting conventions

Treatments will be presented with the following order in the tables: CHF 1535 pMDI, Symbicort® Turbohaler®.

On stratified tables, each stratum will start on a new page.

Unless otherwise specified, frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets.

Unless otherwise stated, listings will be presented by randomised treatment, and sorted by patient ID and visit.

In a listing, in the case that a patient's record has been continued to the next page, an appropriate identification (e.g., the patient ID number) must be presented at the beginning of that page.

In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

In all the listings on safety variables, a column with a flag (§) for treatment misallocation will identify the treatment misallocations.

Re-allocated data will be presented in the listings and identified with a flag (#).

In general, dates will be presented on listings in the format ddmmmyyyy (date9.) and time in the format hh:mm (time5.). In case of partial dates or times, missing information will be replaced by dashes.

13.3 Format

The following information should always be presented:

- 'Clinical Study Code No.:<Study Code No.>' followed by Chiesi denomination in the top portion of each page. Chiesi denomination is 'Chiesi Farmaceutici S.p.A'.
- The table/listing/figure number followed by the title
- The SAS program name followed by the datetime of the output production and the analysis type (e.g. Dry Run; Draft Version; Final Version) in the bottom portion of each page of any table/listing/figure. The source listing/table/dataset will appear bottom left for every table/figure/listing. The analysis set used and SAS Version and the output page number in the format of 'Page x of Y' in the bottom left portion of each page of any table/listing/figure.
- Combined tables and listings will be produced in rich text format (i.e., they will be tabular in format) and organized per sections. These outputs must be provided in both portable format document (.pdf) and rich text format (.rtf).

- Combined PDF and RTF documents must also be provided, including a table of contents with hyperlinks. The combined documents should be divided by document type (tables, figures, listings).
- Complete SAS outputs will be also generated in RTF format for all the tables regarding a statistical model, individually (i.e. one for each statistical table produced). Each rtf file will have the number of the table and a brief description as filename. The combined documents page number in the format of 'Page n of N' will be presented bottom right corner.

The following should be followed for the tables and listings:

- A landscape layout and Letter size will be used.
- A 9-point font size will be used using Courier New font for tables. An 8-point font size will be used using Courier New font for listings.
- Horizontal lines will appear before and after the column heading of the output.
- Additional footnotes may be included if strictly necessary for clarification. Footnotes will be put under the main body of text at the bottom left of the page and will be displayed on each page of the output and not only on the last one.
- The left and right margins will be a minimum of 2.5 cm from the left and 3.0 cm from the right. The top and bottom margins will be a minimum 2.92 cm. Header and footer will be both 1.27 cm.

The following should be followed for the figures:

- A Landscape layout and Letter size will be used.
- A 9-point font size will be used using Courier New font.
- Figures will be produced in RTF and PDF formats (as described above), including relevant titles and footnotes as separate elements on the page (not within the body of the figure).
- Additional footnotes may be included if strictly necessary for clarification. Footnotes will be put under the main body of text at the bottom left of the page and will be displayed on each page of the output and not only on the last one.
- The size of the figures will be: width=15.8 cm, height=10.8 cm. The resolution will be set using the option IMAGE_DPI=400. Figures will have a footer specifying the source table or listing. Figures should clearly identify each treatment arm and require care of colors/symbols.
- The left margin will be a minimum of 2.5 cm, the right margin will be a minimum of 2 cm. The top and bottom margins will be a minimum of 0.8 cm.

13.4 Quality Control

The accuracy and the reliability of the programs and of the outputs are ensured by the validation process as specified in the Chiesi Statistical Programming Cycle SOP (HQRD-SOP-DMSTAT-009).

Briefly, the Statistical Programmer is responsible to draft the Statistical Programming Validation Plan detailing the study specific procedures for executing and documenting the validation of the outputs produced.

The Validator (a Statistical Programmer different from the Programmer developing the program) performs the validation following the instructions available in the Statistical Programming Validation Plan and report the result in the Statistical Programming Validation Report.

14 SAS Code

Linear MMRM for the analysis of the primary efficacy variable:

```
PROC MIXED data = dataset;
    CLASS tmt visit region n_COPD_exac airflow_sev smoking patient;
    MODEL change = tmt visit tmt*visit region n_COPD_exac airflow_sev smoking
    baseline baseline*visit / ddfm=kr;
    REPEATED visit / subject=patient type=un;
    LSMEANS tmt*visit / om at means cl;
    LSMESTIMATE tmt*visit
        'A vs B: Week 4'   1 0 0 0 -1 0 0 0,
        'A vs B: Week 12'  0 1 0 0 0 -1 0 0,
        'A vs B: Week 18'  0 0 1 0 0 0 -1 0/cl;
    LSMESTIMATE tmt*visit
        'A vs B: Week 24'  0 0 0 1 0 0 0 -1/ cl testvalue=-.070 upper;
RUN;
```

Notes:

- *Change* represents the change from baseline to each visit of the variable;
- *Tmt* represents the treatment group;
- *Visit* represents the clinic visit;
- *Region* represents the region (pooled sites as per rule reported in section 12);
- *n_COPD_exac* represents the number of COPD exacerbations in the last year (classified into 2 groups: 1 or >1);
- *Airflow_sev* represents the FEV1% of predicted at screening (<30%, ≥30%)
- *Smoking* represents the smoking status at Screening;
- *Baseline* represents the baseline value of the variable;
- *Patient* represents the Patient Number;
- Treatment order: 1 = CHF 1535 pMDI, 2 = Symbicort® Turbohaler®;
- Only at week 24 the non-inferiority p-value is derived based on the non-inferiority margin of -0.070 L, defined at section 9.1.1.

Calculation of adjusted means (least squares means):

The approach described above (for MMRM and binomial negative) will ensure that the least squares means calculated by SAS will be based on:

- coefficients for classification effects (i.e., the effects of categorical covariates) proportional to the margins observed in the group of patients analysed;
- effects of quantitative covariates set equal to their mean values in the group of patients analysed.

The analysis is based on the following steps:

1. generate a dataset by selecting:
    - in case of repeated post-randomisation measurements (e.g., FEV_1 at each visit, analysed using a linear mixed model for repeated measures): all the post-randomisation records for patients with at least one available and valid post-randomisation measurement and no missing covariates;

- in case of single post-randomisation measurement (e.g., number of COPD exacerbations during the randomised treatment period, analysed using a negative binomial model): all the patients with available and valid response and no missing covariates;

2. in case of repeated post-randomisation measurements, add to the dataset generated in step 1 the records for missing post-randomisation visits of the patients included in the dataset. In the added records the value of the response variable will be missing, but the full information on covariates has to be included;
3. use the dataset obtained as the input dataset for the MIXED or the GENMOD/GLIMMIX procedure, specifying the following options in the LSMEANS statement:
   - in case of repeated post-randomisation measurements: OM AT MEANS;
   - in case of single post-randomisation measurement: OM.

15 References

1. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf
2. Hankinson JL, Eschenbacher B, Townsend M, Stocks J, Quanjer PH. Use of forced vital capacity and forced expiratory volume in 1 second quality criteria for determining a valid test. European Respiratory Journal 2015, 45(5):1283-92.

16 List of Tables, Listings and Figures

16.1 Tables

The raw SAS output for all tables based on statistical models will be provided for internal use only and not for inclusion into the CSR.

Flagged tables below (*) will be provided for Key First Results presentation.

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