PPD International

Chiesi Farmaceutici S.p.A.

Protocol: CCD-05993AA1-14

A 24-week, Double Blind, Double dummy, Randomised, Multinational, Multicentre, 2-arm Parallel Group, active Controlled Clinical Trial of fixed combination of beclometasone dipropionate plus formoterol fumarate plus glycopyrrolate bromide administered via pMDI (CHF 5993) versus the fixed combination of budesonide plus formoterol fumarate (Symbicort® Turbuhaler®) in patients with Chronic Obstructive Pulmonary Disease

Statistical Analysis Plan

PPD Project Number: 229140

SPONSOR SIGNATURE PAGE

Approved by: PPD

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LIST OF ABBREVIATIONS

ADaM	Analysis dataset model
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
β-HCG	Beta-Human Chorionic Gonadotropin
BDP	Beclometasone dipropionate
BDRM	Blinded data review meeting
BMI	Body mass index
BOCF	Baseline observation carried forward
BTR	Best test review
BUD	Budesonide
BUN	Blood urea nitrogen
Ca	Calcium
CAT	COPD assessment test
CI	Confidence interval
Cl	Chloride
COPD	Chronic obstructive pulmonary disease
CS	Clinically significant
CSP	Clinical Study Protocol
CSR	Clinical study report
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
DRP	Data review plan
DRR	Data review report
eCRF	Electronic case report form
EOT	End of Treatment
EQ-5D-3L	Euro Quality of Life – 5 Dimensions – 3 Levels
ETV	Early Termination Visit
FEV_1	Forced expiratory volume in 1 second
FF	Formoterol fumarate
FVC	Forced vital capacity
γ-GT	Gamma-glutamyl transpeptidase
GB	Glycopyrronium bromide
Hb	Haemoglobin
Hct	Haematocrit
HR	Heart rate
IC	Inspiratory capacity
ICU	Intensive Care Unit
IRT	Interactive Response Technology

ITT	Intention-to-treat
K	Potassium
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MAR	Missing at random
$FEF_{25-75\%}$	Forced Expiratory flow
MMRM	Mixed model for repeated measures
Na	Sodium
NCS	Not clinically significant
PLT	Platelets count
pMDI	Pressurised metered dose inhaler
PP	Per Protocol Population
PR	Time interval between the P and R wave in the ECG
PT	Preferred term
QRS	Time interval between the Q and R and S wave
QTcF	Time interval between the Q and T waves corrected for heart rate according to Fridericia's formula
RBC	Red blood cell
RTF	Rich text format
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SDTM	Study data tabulation model
SGRQ	Saint George's respiratory questionnaire
SOC	System organ class
TEAE	Treatment emergent AE
VAS	Visual analogue scale
WBC	White blood cell
WHO	World Health Organisation

RECORD OF MODIFICATIONS

Version Number	Effective Date	Author	TLF Shell ID(s)	Modification Details
0.6	19 January 2017	PPD	Version 0.6	Defined as stable version as confirmed via email by PPD on 23 May 2017
1.0	22 October 2019	PPD	Version 1.0	- Parameter name MMEF was replaced $FEF_{25-75\%}$ to be in line with recent SDTM and spirometry data transfer specification. Reported as change from protocol. Label renamed to "Forced Expiratory Flow". - Clarified that run-in period ends the day before start of randomised treatment period, Section 4.1.15 - The covariate "COPD Severity" defined as FEV1 % of predicted at Screening, <30% or >=30% introduced in all statistical models, where applicable - The calculation of "Average pre-dose morning FEV1" was excluded in descriptive tables and statistical analysis - All statistical models include estimates over the entire treatment period - Algorithm of managing paper diary entries introduced in Section 4.7.2.15 - Corrections and revisions of algorithms / SAS codes in Section 4.16 - Compliance derivation is based on all devices rather than the patient is assigned to. In particular, the formulas in Section 4.5.2 were revised to consider 8 inhalations in total per study day. Previously 4 inhalations were considered only. - General edit corrections - Editorial revisions / corrections - A formal interim analysis introduced with CSP amendment #3 (#4 South Korea version). Details about interim analysis and DMC added. See Sections 4.2 and 4.9.6.

1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease characterized by airflow limitation. It is not fully reversible which is usually both progressive and associated with an abnormal inflammatory response of the lungs to prolonged exposure to noxious particles or gases. Bronchodilators are the mainstay of pharmacologic therapy for COPD and are recommended by international guidelines as first-line therapy in symptomatic patients and those who demonstrate airflow limitation.

Chiesi Farmaceutici S.p.A. developed a fixed combination of Beclometasone Dipropionate (BDP) and Formoterol Fumarate (FF) pressurised metered dose inhaler (pMDI) which has been marketed under the trade name Foster®.

The efficacy and safety of Foster® 100/6 μg per actuation has been demonstrated in adult patients with both moderate or severe persistent asthma and in severe to very severe COPD patients and received marketing authorization in EU.[1], [2]

Currently the marketing authorization for Foster® in Asian Countries includes asthma only.

Chiesi is now developing a triple fixed dose combination for COPD patients by combining Foster® with Glycopyrronium bromide (GB). This triple fixed dose combination is named CHF 5993, or Beclometasone dipropionate/ Formoterol fumarate/ Glycopyrronium bromide, or BDP/FF/GB within this document.

This document presents the statistical analysis plan (SAP) for Chiesi Farmaceutici S.p.A., Protocol No. CCD-05993AA1-14: A 24-week, Double Blind, Double dummy, Randomised, Multinational, Multicentre, 2-arm Parallel Group, active Controlled Clinical Trial of fixed combination of Beclometasone dipropionate plus formoterol fumarate plus Glycopyrronium bromide administered via pMDI (CHF 5993) versus the fixed combination of budesonide plus formoterol fumarate (Symbicort® Turbuhaler®) in patients with Chronic Obstructive Pulmonary Disease.

This analysis plan is based on the following documents:

- final protocol amendment version 3.0 dated 15th March 2019;
- South-Korea specific protocol version 4.0 dated 25th March 2019;
- blank electronic case report form (eCRF) version 4.1 dated 17th September 2018.

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

Note: information regarding the health economic analysis will be reported separately by Chiesi Farmaceutici S.p.A. and does not form part of this SAP.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to demonstrate the superiority of CHF 5993 pMDI over Symbicort® Turbuhaler® in terms of pulmonary function (change from baseline in pre-dose morning Forced Expiratory Volume in 1 Second [FEV_1] and 2-hour post-dose FEV_1 at Week 24).

2.2 Secondary Objectives

Key secondary objective

- To demonstrate the superiority of CHF 5993 pMDI over Symbicort® Turbuhaler® in terms of pulmonary function (change from baseline in pre-dose morning FEV_1 and 2-hour post-dose FEV_1 at Week 24) in the subgroup of Chinese population.

Other secondary objectives

- To evaluate the effect of CHF 5993 pMDI on other lung function parameters, patient's health status and clinical outcome measures;
- To collect data in order to assess the impact of study medication on health economic outcomes;
- To assess the safety and the tolerability of the study medication.

2.3 Primary Efficacy Variables

- Change from baseline in pre-dose morning FEV_1 at Week 24;
- Change from baseline in 2-hour post-dose FEV_1 at Week 24.

2.4 Secondary Efficacy Variables

- Change from baseline in pre-dose morning and 2-hour post-dose FEV_1 at all the other clinic visits;
- FEV_1 response (change from baseline ≥ 100 ml) at Week 24;
- Change from pre-dose to the 2-hour post-dose value of FEV_1 at each visit from Visit 3 onwards;
- Rate of COPD exacerbations over 24 weeks of treatment;
- Time to first COPD exacerbation;
- Change from baseline in pre-dose forced vital capacity (FVC) and inspiratory capacity (IC) at all clinic visits and change from baseline to 2-hour post-dose FVC at all clinic visits;
- Change from pre-dose to the 2-hour post-dose value of FVC at each visit from Visit 3 onwards;
- Pre-dose FEV_1/FVC at all clinic visits;
- Change from baseline in Forced Expiratory Flow ($FEF_{25-75\%}$);

- Change from baseline in the Saint George's Respiratory Questionnaire (SGRQ) total score and domain scores at clinic visits 4 and 6;
- SGRQ response (change from baseline in total score ≤- 4) at Week 24;
- Change from baseline in COPD Assessment Test (CAT) at all clinical 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).

2.5 Health economic variables

- Euro Quality of Life – 5 Dimensions – 3 Levels (EQ-5D-3L) visual analogue scale (VAS) score and EQ-5D-3L index at clinic visits 2, 4 and 6;
- Number of hospital admissions due to COPD and other causes;
- Number of days with oxygen therapy use due to COPD;
- Unplanned diagnostic or instrumental tests performed due to COPD;
- Mortality.

2.6 Safety Assessments

- Adverse Events (AEs) and Adverse Drug Reactions (ADRs);
- Vital signs (systolic and diastolic blood pressure);
- 12-lead ECG parameters: heart rate (HR), the time interval between the P and R wave (PR), the time interval between the Q and R and S wave (QRS), and the time interval between the Q and T waves corrected for HR according to Fridericia's formula (QTcF) (baseline, pre-dose and 10 min post-dose at Week 12 and Week 24);
- Standard Haematology and Blood Chemistry.

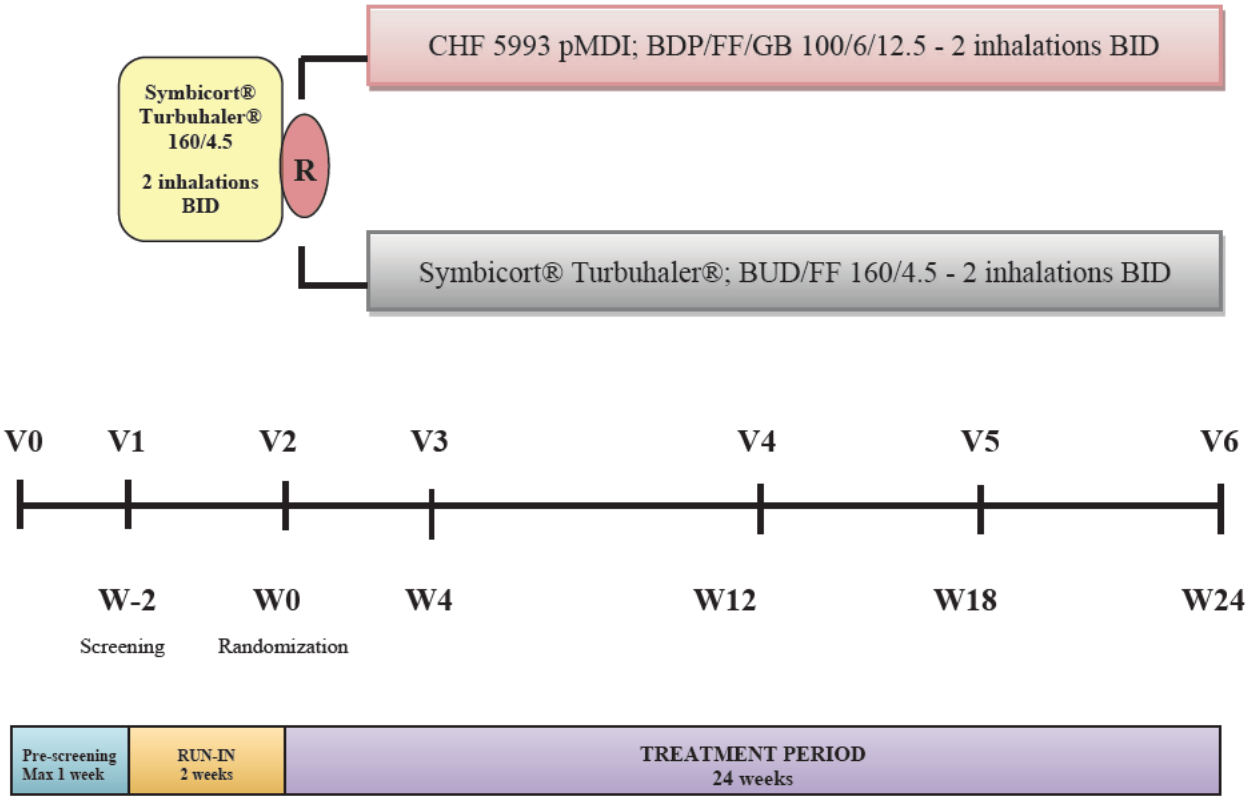
3 STUDY DESIGN / INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a phase III, double-blind, double-dummy, randomised, multinational, multicenter, 2-arm parallel-group, active-controlled study. Approximately 60 sites will be involved.

The study duration for each patient will be up to 27 weeks as depicted below:

Figure 1: Study Design



During the run-in period, all patients will receive Symbicort® Turbuhaler® 160/4.5 µg per inhalation, 2 inhalations BID. Eligible patients will then be randomised to one of two treatments as described above.

3.2 Study Treatments

3.2.1 Run-in Period (from V1 to V2)

Symbicort® Turbuhaler® 160/4.5 µg/unit	2 inhalations BID Total daily delivered dose: Budesonide 640 µg plus FF 18 µg.

3.2.2 Randomised Treatment Period (from V2 to V6)

Test product

CHF 5993 pMDI 100/6/12.5 µg	2 inhalations BID plus 2 inhalations BID of Symbicort® Turbuhaler® placebo Total daily metered dose: BDP 400 µg plus FF 24 µg plus GB 50 µg.

Control product

Symbicort® Turbuhaler® 160/4.5 µg/unit:	2 inhalations BID plus 2 inhalations BID of CHF 5993 pMDI placebo Total daily delivered dose: BUD 640 µg plus FF 18 µg.

3.2.3 Rescue Medication

Salbutamol will be used as rescue medication. Patients will take the rescue medication on an as-needed basis.

3.3 Study Schedule

A total of 7 clinic visits (Visit 0 to Visit 6) will take place during the study, plus a follow-up phone call, as follows:

- **Visit 0 (V0)**: Pre-screening visit to explain the aim of the study to the patients, to obtain their informed written consent and to prepare patients for V1;
- **Visit 1 (V1)**: Screening visit (within 7 days after V0) to verify the patients' eligibility. This visit will be followed by a 2-week run-in period, where the patients will receive open-label Symbicort® Turbuhaler®;
- **Visit 2 (V2)**: randomisation visit when patients will be randomised to one of the 2 treatment arms;
- **Visit 3 (V3)**: after 4 weeks of treatment;
- **Visit 4 (V4)**: after 12 weeks of treatment;
- **Visit 5 (V5)**: after 18 weeks of treatment;
- **Visit 6 (V6)**: after 24 weeks of treatment;
- **Follow-up phone contact (for completed and discontinued patients)**: after 7-10 days of last study medication intake or the Early Termination visit in order to check the status of any unresolved AEs at the last visit.

A "window" of -3 to + 3 days is allowed for the dates of the visits from V2 to V6.

Note: unscheduled visits can be performed during the study at the discretion of the Investigator. The relevant information will be collected in the eCRF.

The study plan and scheduled tests are summarized in the following Schedule of events:

Table 1: Schedule of events

	Pre-screening	Screening	Treatment Period					
Visits	V 0	V 1	V 2*	V 3	V 4	V 5	V6 / ETV**	FU call***
Time (Weeks)	Wk -3	Wk -2 (within 7 days after V0)	Wk 0 (±3 days)	Wk 4 (±3 days)	Wk 12 (±3 days)	Wk 18 (±3 days)	Wk 24 (±3 days)	
Informed consent procedures	✓							
Demographic data	✓							
Instructions for the screening visit	✓							
Patient card	✓							
Inclusion/Exclusion criteria		✓						
Eligibility confirmation for randomisation			✓					
Medical history/Previous medications		✓						
Concomitant medications		✓	✓	✓	✓	✓	✓	
Physical examination		✓	✓	✓	✓	✓	✓	
Weight and height		✓						
Smoking status		✓	✓	✓	✓	✓	✓	
Vital signs (Blood Pressure) at pre-dose and 10 min post-dose		✓[1]	✓	✓	✓	✓	✓	
12-lead ECG pre-dose and 10 min post-dose		✓[1]	✓[2]		✓		✓	
Post-salbutamol spirometry[3]		✓						
Lung function measurements at clinic visits: pre-dose and 2h post-dose spirometry[4]		✓[1]	✓	✓	✓	✓	✓	
Assessment of COPD exacerbations		✓	✓	✓	✓	✓	✓	
Training to the use of Turbuhaler inhaler		✓	✓					
Training to the use of pMDI inhaler and of spacer		✓	✓					
CAT		✓	✓	✓	✓	✓	✓	
EQ-5D-3L Health Questionnaire			✓		✓		✓	
Health economic assessment			✓	✓	✓	✓	✓	
SGRQ			✓		✓		✓	
Daily diary dispensing[5]		✓	✓	✓	✓	✓		
Daily diary returning[5]			✓	✓	✓	✓	✓	
Haematology – Blood chemistry		✓			✓	✓	✓	
Serum pregnancy test[6]		✓					✓	
Urinary pregnancy test[6]		✓	✓	✓	✓	✓		
Interactive Response Technology (IRT) call/connection	✓	✓	✓	✓	✓	✓	✓	
Drug dispensing		✓	✓	✓[7]	✓	✓[7]		
Drug returning			✓	✓[7]	✓	✓[7]	✓	
Adverse events/Serious adverse events		✓	✓	✓	✓	✓	✓	✓

*Randomisation / **ETV: Early Termination Visit for randomised patients withdrawn before Wk 24
*** after 7-10 days from last study medication intake / Early Termination

1. At screening, only pre-bronchodilator
2. Triplicate pre-dose ECG
3. at least 10-15 min after 4x100 μg salbutamol. It can be repeated once before Visit 2 if the inclusion criterion no. 4 (refer to protocol section 4.2) is not met at V1.
4. At V1 pre-bronchodilator spirometry including FEV_1, FVC, $FEF_{25-75\%}$, IC will be carried out and FEV_1 + FVC will be measured 10-15 minutes after salbutamol intake. From V2 to V6 a pre-dose spirometry including FEV_1, FVC, $FEF_{25-75\%}$ and IC will be carried out. Post dose spirometry after 2 hours will only assess FEV_1 and FVC. Wash-out of rescue medication (at least 6h) or run-in/study medication must be respected in the morning of the visit for the pre-dose measurements.
5. For the recording of daily use of study (run-in and treatment period) and rescue medication
6. For females of childbearing potential only
7. Temporary return and re-dispensing of medication dispensed during the previous visit

Early Termination Visit (for a patient withdrawn before Week 24)

In case of early study discontinuation, all the pre-dose procedures scheduled for Visit 6 (Week 24 / End of Treatment Period) will be performed.

If a patient is withdrawn before the end of treatment period, a final evaluation will be done.

The Investigator must fill in the Early Termination Visit in the eCRF. The explanations regarding the reasons of withdrawal and all the assessments performed will be recorded.

Follow-up phone contact

Within 7 days after the last study medication intake (Visit 6) or the Early Termination Visit, the patients will be contacted by phone and the status on all unresolved AEs at the last visit will be checked and recorded.

The Investigator will access IRT to record the study completion/discontinuation for the patient.

3.4 Concomitant Medication

Section 5 of the protocol details permitted/non-permitted concomitant medications.

3.5 Study Analysis Populations

The following analysis populations are defined:

3.5.1 Safety Population

The safety population is defined as all unique randomised patients who receive at least one administration of the study medication. If a patient is unintentionally randomized twice in the study, only the data collected from the initial randomisation site will be considered for analysis.

Data from the randomization at the second site will not be included in the analysis (but documented and reported in listings, see section 3.5.4).

3.5.2 Intention-to-Treat Population (ITT)

The ITT population is defined as all unique randomised patients who receive at least one administration of the study medication and with at least one available evaluation of efficacy after the baseline. If a patient is unintentionally randomized twice in the study, only the data collected from the initial randomisation site will be considered for analysis.

Data from the randomization at the second site will not be included in the analysis (but documented and reported in listings, see section 3.5.4)

3.5.3 Per Protocol Population (PP)

The PP population is defined as all patients from the ITT population 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 blinded data review meeting (BDRM) and described in the Data Review Report (DRR).

3.5.4 Other Populations Defined for Tables and Listings

For the purposes of tables, additional three populations are defined:

- All screened patients;
- Randomised population (all randomised patients)
- Screening failure patients.

For the first two populations, in case a subject is unintentionally randomized twice in the study, the subject will be included in the analysis with the ID from the site where the initial randomization took place, while data from the randomization at the second site will not included in the analysis.

For the purposes of listings, additional three populations are defined:

- All screened patients;
- Randomised population (all randomised patients)
- Screening failure patients.

For the first two populations, in case a subject is unintentionally randomized twice in the study, both information coming from the two different ID will be reported in the listings (with appropriate flag to identify the second ID).

3.6 Withdrawn Patients

If a patient is withdrawn/drops-out of the study after receiving any study medication, the patient study number and corresponding study medication will not be reassigned to another patient.

3.7 Randomisation

A balanced block randomisation scheme stratified by Country will be prepared via a computerised system. Patients will be centrally assigned, in each centre, to one of the two treatment arms at the end of the run-in period through an Interactive Response Technology (IRT) system.

The Investigators at the sites will connect to the IRT to enrol and randomise patients. The IRT will allocate the patient ID (number of nine digits: the 3 first digits correspond to the ISO country code, the next 3 digits will identify the site incrementally and the 3 last digits will be chronologically be assigned to patients within a centre), will assign the patient to a certain treatment group using a list-based randomisation algorithm and will assign the study medication kit number corresponding to the treatment group assigned to the patient.

3.8 Blinding

The randomisation list will not be available to patients, Investigators, monitors or employees of the centre involved in the management of the trial before unblinding of the data. The Sponsor's clinical team will also be blinded during the study as they will not have direct access to the randomisation list.

In case of emergency, unblinding of the treatment code will be done through IRT.

For the interim analysis, only the data of the patients included in the interim evaluation (which comprise of completed or discontinued patients only) will be unblinded. The patients included in the interim analysis will be clearly identified and documented in the DRR which will be finalized prior to the unblinding for the interim analysis.

The unblinding will be organized and managed by an unblinded team at PPD which is separate from the study team. This unblinded team will receive the treatment codes directly from the IRT provider, run the analysis and release the unblinded results to the Data Monitoring Committee (DMC) only. The Sponsor's clinical team, PPD study team as well as patients, Investigators, monitors and employees of the centres involved in the management of the trial will remain blinded.

DMC will gather and review the unblinded output, evaluating the evidence provided (see Section 4.2). If, based on the recommendation from DMC, the Sponsor will decide:

- to stop the patients' recruitment, PPD study team and Sponsor's clinical team will be unblinded with respect to the interim analysis population only. Patients who were not part of the interim analysis population will remain blinded until the final database lock and final unblinding;
- to continue the patients' recruitment, PPD study team and Sponsor's clinical team will remain blinded until the final database lock and final unblinding.

Further details on the unblinding process are included in the Blinding Maintenance Plan.

3.9 Sample Size

The sample size has been calculated to demonstrate the superiority of CHF 5993 pMDI over Budesonide/formoterol in terms of change from baseline in pre-dose morning FEV_1 and change from baseline to the 2-hour post-dose value of FEV_1 at Week 24 in the overall study population and in the Chinese population.

A total of 990 patients (495 patients per group) will be randomised in order to reach a total of 832 evaluable patients at Week 24 (416 per group), considering a non-evaluable rate of approximately 16% at this time point.

The study is planned to recruit 75% of patients in China and 25% of patients in Korea and Taiwan (with at least 96 patients randomized in Taiwan in order to reach at least 80 evaluable Taiwanese patients).

This sample size will provide:

- approximately 93.3% power to detect a mean difference of 60 ml in favour of CHF 5993 pMDI in change from baseline in pre-dose morning FEV_1 at a two-sided significance level of 0.05, assuming a standard deviation (SD) of 250 ml;

- approximately 98.1% power to detect a mean difference of 70 ml in favour of CHF 5993 pMDI in change from baseline to the 2-hour post-dose value of FEV_1 at a two-sided significance level of 0.05, assuming a SD of 250 ml.

An overall study power for the primary efficacy analysis of approximately 91.5% will therefore be ensured.

Under the assumptions of 75% of patients recruited in China (742 randomized, 624 evaluable), this sample size will provide:

- approximately 85% power to detect a mean difference of 60 ml in favour of CHF 5993 pMDI in change from baseline in pre-dose morning FEV_1 at a two-sided significance level of 0.05, assuming a SD of 250 ml;
- approximately 93.8% power to detect a mean difference of 70 ml in favour of CHF 5993 pMDI in change from baseline to the 2-hour post-dose value of FEV_1 at a two-sided significance level of 0.05, assuming a SD of 250 ml.

An overall power for the primary efficacy analysis in the subgroup of Chinese population of approximately 80% will therefore be ensured.

The sample size for the interim analysis is planned to be based on the following assumptions (reflecting blinded data information collected during the study):

- mean difference between CHF 5993 pMDI and Budesonide/formoterol in the change from baseline in pre-dose morning FEV_1 and 2-hour post-dose FEV_1 at Week 24: same assumptions as in the initial sample size estimation above (60 and 70 mL, respectively);
- SD for both endpoints: 200 mL;
- non-evaluable rate at Week 24: 13%;
- about 81% of patients enrolled in China and 19% in Taiwan and South Korea.

To avoid an inflation of the Type I error, the significance level will be adjusted using the Pocock-type error spending function method. Refer to Section 4.2 for further details.

In order to ensure in the interim analysis a power of approximately 89% for the primary efficacy endpoints in the overall study population, a total of 614 patients should be randomised in order to reach 534 evaluable patients at Week 24.

A total of 499 Chinese patients should be randomized in order to have 434 evaluable Chinese patients that would allow a power of approximately 80% for the primary efficacy endpoints in this population, in line with the original sample size calculation.

Power was calculated assuming a two-sided significance level of 0.0372 at the interim analysis (calculated estimating an inclusion of 534 / 832 = 64.2% of the evaluable patients in the interim analysis).

4 STATISTICAL METHODS

All report outputs will be produced using SAS® version 9.3 in a secure and validated environment. All tables, figures and data listings to be included in the CSR will be independently checked for consistency, integrity and in accordance with standard PPD procedures.

4.1 Conventions Used in the Analyses

4.1.1 Populations for Analysis

Demographic and baseline characteristics will be summarised in the Safety, ITT and PP populations, with the following exceptions:

- CAT, SGRQ, the variables derived from diary data and the health economic variables will be summarised in the ITT population only;
- the medical history and the concomitant diseases will be summarised in the Safety and ITT populations;
- the prior and concomitant medications will be summarised for the ITT population only;
- the safety variables will be summarised in the Safety population only.

Since the superiority of CHF 5993 pMDI over Budesonide/formoterol will be tested, the primary efficacy analyses will be based on the ITT population. These analyses will be also performed on the PP population for sensitivity purposes.

The secondary efficacy variables and the health economic variables will be analysed in the ITT population.

The safety variables will be analysed in the Safety population.

The primary and secondary efficacy variables as well as all safety variables will be tested in the overall and then by Country.

For the populations to be considered in the stratified analyses, see section 4.1.5 below.

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

- the patient will be reported under the randomised treatment group in all data listings and for all analyses performed on the randomised population and on the ITT population (and in listings on all screened patients);
- the patient will be reported under the randomised treatment group for all analyses performed on the PP population. However, in case of relevant duration of the period affected by treatment misallocation, the patient will be excluded from the PP population;
- the patient will be reported under the treatment actually received for all analyses performed on the safety population. 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 BDRM and the decisions on the inclusion of study populations will be documented in the DRR. All the cases of treatment misallocation will be reported in a data listing.

4.1.2 Treatment Groups

If not stated otherwise tabulations will be presented by treatment groups:

- CHF 5993 pMDI;
- Budesonide/formoterol;
- Overall (not applicable for compliance, concomitant and post-study medications, efficacy and safety analyses).

4.1.3 Descriptive statistics

Descriptive statistics for quantitative variables will include n (the number of non-missing values), arithmetic mean, SD, median, minimum, maximum values, and the 95% confidence interval (CI) of the arithmetic mean. The 1st and the 3rd quartiles will be also presented for the EQ-5D-3L VAS score and the EQ-5D-3L index.

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.

4.1.4 Statistical Significance

Hypothesis testing will be carried out using a two-sided alpha=0.05 level. Refer to Section 4.2 for the adjusted alpha levels to be considered at the interim and the final analysis of the primary efficacy variables, ensuring an overall two-sided alpha=0.05 level.

4.1.5 Stratified Analyses

The demographic characteristics and the medical/surgical history and concomitant diseases will be also summarised on the Safety population stratifying by:

- Country (China, Korea, Taiwan);
- age (<65, 65-74 or ≥75 years).

The analysis of change from baseline in pre-dose morning FEV_1 to each clinic visit and change from baseline to the 2-hour post-dose value of FEV_1 at each clinic visit will be also performed on the ITT population (also PP population for the stratification by country) stratifying by:

- Country (China, Korea, Taiwan);
- severity of airflow limitation (post-bronchodilator FEV1 at screening <30% or ≥30% of the predicted normal value).

All the secondary efficacy analysis will be also performed on the ITT population stratifying by Country (China, Korea, Taiwan), with the exception of FEV_1 responder analysis, which will be conducted also for the PP population.

AEs and pneumonias as well as other safety variables (Vital signs, ECG and laboratories) will be analysed on the Safety population stratifying by Country (China, Korea, Taiwan).

Exposure and Summary of Treatment Emergent Adverse Events tables will be also stratified by age (<65, 65-74 or ≥75 years).

Health Economic variables will be analysed on the ITT population and stratified by Country.

4.1.6 Definition of Baseline

With the exception of efficacy variables derived from diary data and laboratory parameters, baseline values are those recorded at Visit 2 prior to randomisation.

For the efficacy variables derived from diary data, baseline values are the averages/percentages recorded during the run-in period.

For the laboratory parameters, baseline values are those recorded at screening.

4.1.7 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.

4.1.8 Date of First/Last Randomised Study Medication Intake

The date of first randomised study medication intake is the earliest date of randomised study medication intake considering both the eCRF and the diary data.

The date of last randomised study medication intake is the date of last study medication intake recorded in the Study Termination form of the eCRF.

4.1.9 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. Since many algorithms used in the statistical analysis requires the start of the randomised treatment period to be identified, an ad-hoc variable specifying this date will be defined. 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 BDRM and documented in the Data review plan (DRP).

  As a consequence, the distinction between diary data from the run-in and the treatment period will not be based on the EPOCH variable included in the SDTM datasets, but on the algorithms defined in the SAP.

- The date of end of randomised treatment period will be initially set according to the following rules:

  1. if the follow-up contact was recorded, then the date of end of randomised treatment period will be defined as the most recent of the following dates: dates of clinic visits

(including early termination and unscheduled visits, but excluding the follow-up contact), date of last randomised study medication intake (see the previous section);

2. if the follow-up contact was not recorded, then the date of end of randomised treatment period will be defined as the most recent of the following dates: dates of clinic visits (including early termination and unscheduled visits), date of last randomised study medication intake (see the previous section), date of completion/discontinuation.

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

4.1.10 Data Re-allocation

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

- Data collected at multiple visits (spirometry, SGRQ, CAT, health economic data, vital signs, ECG and laboratory data) recorded at the study termination visit for discontinued patients will be re-allocated by selecting the visit following the last one performed before the study termination visit with the expected date closest to the date of the study termination visit. For example, if the last visit performed before the study termination visit was Visit 4, the data recorded at the study termination visit will be re-allocated to Visit 5 or 6 depending on the date of the study termination visit. If the study 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 ECG data and SGRQ can be re-allocated only to Visits 4 and 6 and laboratory data to only Visits 4, 5 and 6.
- for discontinued patients, efficacy data recorded in the diaries (i.e. use of rescue medication) from the last visit performed before the study termination visit or the date of discontinuation onwards will be re-allocated 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 re-allocated to the next expected inter-visit period.
- in case of missing intermediate visit not due to the re-allocation of data collected at the study termination visit (e.g., Visit 4 missing, but Visits 3 and 5 performed), the possibility of imputing an expected date for the missing visit in order to define the inter-visit periods for diary data will be evaluated case by case during the blind data review and discussed at the BDRM.

In general, unscheduled/optional assessments will not be included in by-visit summaries but only listed.

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 for spirometry and ECG assessments only:

- two or more spirometry's valid for the same time point (with the time point 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;
- multiple 12-lead ECG measurements associated to the same time point (with the time point checked vs. the time of medication intake):
  - the average value will be considered for HR, QTcF, PR and QRS. If at least one of the abnormalities listed in section 4.1.12 will be found in at least one of the measurements on which the average has to be calculated, the numerical parameters obtained in all the considered measurements will be excluded from the statistical analysis;
  - all the abnormalities identified in the considered measurements will be jointly considered in the analysis.

The following rules to handle unscheduled/optional assessments will be considered for ECG and laboratories assessments for assessments performed before Visit 2 (or before the first intake of study medication for laboratories), but in dates different from Visit 1 date:

- 12-lead ECG:
  - the last pre-dose assessment before Visit 2 with non-missing result should be considered as from Visit 1 in the analysis (with the time point checked vs. the time of run-in medication intake);
- laboratories:
  - the last assessment before first study drug intake of each parameter should be considered as from Visit 1 in the analysis. For WBC and the differential count parameters (lymphocytes, neutrophils, monocytes, eosinophils, basophils) the last complete assessment (i.e., with available measurements for all these parameters) before first study drug intake should be considered in the analysis. If no complete assessment is available, the last assessment before first study drug intake with the highest number of available parameters should be considered in the analysis.

Potential issues of the approach above defined and other decisions regarding data re-allocation will be evaluated during the BDRM and documented in the DRR.

4.1.11 Diary Data

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

4.1.12 Exclusion of Data from the Statistical Analysis

12-lead ECG numerical parameters (HR, QTcF, PR and QRS) will not be included in the statistical analysis in the following cases:

- patients with a pacemaker already in place at study entry, 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 assistance device user";
- patients with a pacemaker implanted during the study, identified by a procedure coded with the Preferred Term "Cardiac pacemaker insertion" (other relevant cases may be identified in the Data Review Report). In this case, only the parameters assessed in a date $\geqslant$ start date of the procedure will be excluded from the statistical analysis.

In addition, for patients without a pacemaker the 12-lead ECG numerical parameters measured at a specific time point will be excluded from the statistical analysis if at least one of the following abnormalities will be detected at that time point:

- Atrial fibrillation: Atrial fibrillation, Possible atrial fibrillation
- Atrial flutter: Atrial flutter, Possible atrial flutter
- Ectopic supraventricular rhythm: All the other abnormalities recorded in the 'Supraventricular Arrhythmias', excluding the ones reported above.
- Complete heart block: 3rd degree AV block, Possible 3rd degree AV block

Single 12-lead ECGs (i.e., at a specific time point) will be also excluded from the statistical analysis if PR=0 (since this is an indication of an unreliable ECG). Of note, not only PR but also all the other numerical parameters (QTcF, PR and QRS) will be excluded from the analysis in this case. If for a time point several ECGs are available due to optional/unscheduled assessments, only the ones with PR=0 will be excluded.

For the triplicate 12-lead ECG performed at Visit 2 pre-dose, if at least one of the abnormalities listed above will be found in at least one measurement, the numerical parameters obtained in all three measurements will be excluded from the statistical analysis (also, their average at the individual level will not be calculated).

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 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 time point will be excluded).

Patients data recorded for routine safety evaluations after study termination will not be analysed nor listed, except for SAEs (see Section 10.8 of the clinical study protocol). It is agreed that equipment provided by vendor can be used for safety evaluations at any time, including time points beyond study termination; this information is collected after the end of the study and is not covered by the informed consent. For this reason, the data will be kept out from the outputs. The data will be still maintained in the study data tabulation model (SDTM) and analysis dataset model (ADaM) datasets, as the Vendor is not able to remove those records.

A final confirmation of ECG abnormalities leading to exclusion of ECG parameters measured at a specific time point from the statistical analysis will be made at the BDRM.

In case of data excluded from the statistical analysis (in the situations above described but also in other cases, for example: spirometry tests excluded due to technical issues, or data excluded due to study termination visit performed at discontinuation not re-allocated), 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 measurement at Visit 2 is excluded. In the responder analysis, values excluded from the analysis will be considered as missing values. Regarding the calculation of average pre-dose morning FEV_1, see section 4.7.1.1.

4.1.13 Spirometry at Visit 1

If inclusion criterion no. 4 was not met at Visit 1 (or Visit 1 spirometry is not available) and the spirometry was repeated before Visit 2, the 2nd assessment 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). Data transferred from BMS (in the SAP, we will refer to these data as the "centralised spirometry data") and not eCRF data will be used.

4.1.14 Listings

All data collected in the eCRF will be presented in the listings. All the data derived from the diaries used in the analyses will be presented in the listings.

4.1.15 Definition of Study Periods

Screening Period

The screening period is starting with the date of ICF and ends at the day before starting the run-in period (Visit 1).

Run-in Period

The run-in period is defined as: starting from the morning of the day of the Visit 1 to the day before the start of randomised treatment period. This period definition applies to compliance purposes as well which will be derived from diary data.

Randomised Treatment Period

The randomised treatment period is defined as detailed in Section 4.1.9.

4.2 Interim Analysis

A single unblinded interim analysis for superiority will be performed on 614 randomised patients (**534** evaluable patients, of whom **440** recruited from China. A patient will be considered evaluable in case of availability of both the primary efficacy variables (change from baseline in pre-dose and 2-hour post-dose FEV_1 at Week 24).

An independent DMC will give advice for continuing or stopping the study recruitment based on the results of all statistical analyses as described in this SAP (see Section 4.9.6 for details on the responsibilities of the DMC).

A brief overview of the findings required to demonstrate superiority of CHF 5993 pMDI over Budesonide/formoterol in terms of the primary efficacy variables (see Section 4.7.1) overall and in the subgroup of patients in the Chinese population is given below. A statistically significant

mean difference between the treatments favouring CHF 5993 pMDI must be found in all the following comparisons to confirm its superiority over Budesonide/formoterol:

- change from baseline in pre-dose morning FEV1 at Week 24 in the overall population;
- change from baseline in 2-hour post-dose FEV1 at Week 24 in the overall population;
- change from baseline in pre-dose morning FEV1 at Week 24 in the Chinese population;
- change from baseline in 2-hour post-dose FEV1 at Week 24 in the Chinese population.

4.2.1 Group Sequential Procedures

The primary efficacy variables will be tested at a two-sided overall significance level of 0.05.

In order to ensure this overall significance level, the boundaries on the p-value scale to reject the null hypothesis of no difference between treatments in the interim and final analyses will be based on the Pocock-type error spending function method [4] and calculated with SAS® version 9.4 under the responsibility of the Sponsor using the following code:

```
PROC SEQDESIGN ERRSPEND BOUNDARYSCALE=PVALUE;
   DESIGN METHOD=ERRFUNCPOC
   NSTAGES=2 ALPHA=0.05
   ALT=TWOSIDED STOP=REJECT
   INFO=CUM(0.642 1);
RUN;
```

In the above SAS code, **0.642** is the ratio (information fraction) between the number of evaluable patients (availability of both changes from baseline in pre-dose and 2-hour post-dose FEV_1 at Week 24) in the overall population included in the interim analysis (**534**) and the expected total number of evaluable patients in the overall population (**832**). Of note, the boundaries for the one-sided p-value are provided by the above SAS code. The boundaries for the two-sided p-value are obtained by multiplying by 2 the boundaries calculated by SAS.

Based on a total of 534 and 832 (expected) evaluable patients included in the overall population for the interim and final analyses, respectively, the following boundaries will be considered for the two-sided p-value:

Analysis stage	No. of evaluable patients in the overall population	Boundary for the two-sided p-value
Interim	**534**	**0.0372**
Final	832 (expected)	**0.0250**

At each stage, in the primary efficacy comparisons statistical significance will be declared in case of two-sided p-value < boundary (as above calculated).

Of note, in case of successful interim analysis an additional analysis including all the patients included in the interim analysis and the randomised patients that did not contribute to the interim analysis will be performed (these will be followed up to study completion or discontinuation). The same boundary used in the interim analysis (**0.0372**) will be considered for statistical testing.

In case of a number of evaluable patients in the overall population at the time of the final analysis different from the expected one (832):

- if the actual number of evaluable patients will be < 832 ("underrunning"), then the pre-specified boundary based on 832 evaluable patients will be considered. This is a conservative approach in this scenario [5];
- if the actual number of evaluable patients will be > 832 ("overrunning"), then the boundary will be adjusted accordingly to the approach described below.

Under the null hypothesis of no treatment difference, the joint distribution of the standardized test statistics for the interim and final analyses (Z_1 and Z_2, respectively) is bivariate normal with [6]:

- $E(Z_i) = 0$ and $Var(Z_i) = 1$ for $i = 1, 2$;
- $Cov(Z_1,Z_2) = Corr(Z_1,Z_2) = \sqrt{(N_1/N_2)}$, where N_1 is the number of patients included in the interim analysis and N_2 is the number of patients included in the final analysis.

The critical values for the standardized test statistics defined for the interim and final analyses (c_1 and c_2, respectively) should ensure the control of the overall two-sided significance level α. Therefore, under the null hypothesis, the following relationship must hold:

$$\alpha/2 = Pr(Z_1 > c_1 \text{ or } Z_2 > c_2) = 1 - Pr(Z_1 \leq c_1 \text{ and } Z_2 \leq c_2).$$

In the "overrunning" scenario, $\alpha/2$ and c_1 are fixed at their pre-specified values, while c_2 should be derived based on the above relationship. This derivation will be based on the following steps.

Step 1

c_1 will be derived by using the above SAS code for the SEQDESIGN procedure, by requiring the boundary to be expressed on the standardized test statistic scale (option *BOUNDARYSCALE=PVALUE* to be replaced by *BOUNDARYSCALE=STDZ*). As c_1 corresponds to the boundary (implicitly) considered at the interim analysis, the expected ratio between the numbers of evaluable patients in the overall population N_1/N_2 at the time of the interim analysis (i.e., not the actual one observed at the final analysis) will be considered.

Step 2

c_2 and the corresponding boundary on the two-sided p-value scale will be calculated using the following SAS code:

```
DATA boundary;
   corr=SQRT(ratio_act);
   c2=1.96;
   DO UNTIL(alpha<.025);
      alpha=1-PROBBNRM(c1,c2,corr);
      c2+.000001;
   END;
   pvalue2=2*PROBNORM(-c2);
RUN;
```

In the above SAS code:

- ratio_act should be replaced by the actual ratio between the numbers of evaluable patients in the overall population N_1/N_2 observed at the final analysis;

- c1 should be replaced by the value calculated in the previous step;
- the value for the variable pvalue2 calculated in the data step corresponds to the adjusted boundary on the two-sided p-value scale to be considered in the final analysis.

Of note, all the procedures described in this section are based on the following assumptions:

- the number of patients with available data will be almost identical for the two primary efficacy variables;
- the ratio between the number of evaluable patients included in the interim and the final analyses will be very similar for the overall population and for the Chinese population;
- the contribution to the primary efficacy comparisons of patients with missing data at Week 24 (also incomplete FEV_1 profiles will be considered in the analyses based on linear mixed models for repeated measures) will be limited and in any case comparable for both treatments.

All results of calculations above will be printed and appended to this SAP before finalization.

4.3 Disposition of Patients

The number of patients screened, the number screen failures and the number of patients with each reason for screen failure will be presented overall and by Country. All patients will be included. T14.1.1.1

The number of patients randomised at Visit 2, who attended Visits 3, 4 and 5, who completed Visit 6 and who performed Visit 6 assessments but discontinued will be presented by treatment group using the Randomised population. The Follow-up call will be presented as well. T14.1.1.2

The number of patients screened, randomised and completed will be also presented by Country and by site. T14.1.1.3, T14.1.1.4

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 withdrawal from the study will be presented by treatment group using the Randomised population. T14.1.2.1

Time to discontinuation from the study after randomisation will be analysed using the Kaplan-Meier method for the Randomised population. For the study periods T14.1.2.2, F14.1.1

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

the number of patients in the 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. A comparison between treatments will also be performed by means of the log-rank test. Plot of time to discontinuation (failure time) by treatment group will also be presented.

Major and minor protocol deviations will also be summarised by treatment group using the ITT population. T14.1.3.1, T14.1.3.2

The number of patients included in each of the Randomised, Safety, ITT and PP populations will be summarized for each treatment group and overall. The summary will also be presented by Country. T14.1.4.1

Notes:

- Time to discontinuation from the study (weeks) will be calculated as (date of completion/discontinuation – date of start of randomised treatment period)/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.

4.4 Baseline and Demographic Characteristics

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

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

4.4.1 Demography/Baseline Characteristics

Demographic and baseline characteristics will be summarised by treatment group and overall. This will include age, sex, race, height, weight, BMI. Separate summaries will be produced using the Safety, ITT and PP populations. The same summary will be also presented stratifying as detailed in Section 4.1.5. T14.1.5.1-T14.1.5.4

Notes:

- BMI will be calculated as: weight at the visit 1 (kg)/height at visit 1 $(m)^2$. In case of missing weight and/or height at Visit 1, the last measurement taken before randomisation (during unscheduled visit) will be considered for the calculation of BMI; if also considering pre-randomisation unscheduled visits no sufficient information are available to compute the BMI, this parameter will not be calculated.

4.4.2 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 populations. T14.1.6.1, T14.1.6.2, T14.1.6.3

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.

4.4.3 COPD History

Time since first COPD diagnosis (years), main COPD phenotype (chronic bronchitis only, emphysema only, chronic bronchitis + emphysema), COPD medication category at study entry (ICS/LABA, ICS/LAMA, LABA/LAMA, LAMA, LABA), spacer device use before study entry, spacer device use during study, number of COPD exacerbations in the previous year (as a continuous and categorical variable [1, 2, 3, >3]), time since last documented COPD exacerbation (months), treatment for the last documented COPD exacerbation (systemic corticosteroids only, antibiotics only, systemic corticosteroids and antibiotics, no systemic corticosteroids / no antibiotics), hospitalisation/emergency room for the last documented COPD exacerbation will be presented by treatment group and overall. Separate summaries will be produced using the Safety, ITT and PP populations. T14.1.7.1, T14.1.7.2, T14.1.7.3

Notes:

- Spacer device use before Study Entry will be based on the "COPD History" form of the eCRF;
- Time since first COPD diagnosis (years) will be calculated as (date of Visit 1 – date of first COPD diagnosis)/365.25;
- Time since last documented COPD exacerbation (months) will be calculated as (date of Visit 1 – date of last documented COPD exacerbation)/30.4375.

4.4.4 Spirometry at Visit 1 and at Visit 2 Pre-dose

The following spirometry parameters will be summarised by treatment group and overall: T14.1.8.1, T14.1.8.2, T14.1.8.3, T14.1.8.4, T14.1.8.5, T14.1.8.6

- Visit 1: FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$ 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 $FEF_{25-75\%}$ post-salbutamol intake; reversibility in FEV_1 (L), reversibility in FEV_1 (%) [as a continuous and categorical variable (≤12%, >12%)];
- Visit 2: FEV_1, FVC, $FEF_{25-75\%}$ and IC pre-dose.

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

Notes:

- reversibility in FEV_1 (L) will be calculated as FEV_1 post-salbutamol intake – FEV_1 pre-salbutamol intake;
- reversibility in FEV_1 (%) will be calculated as 100*(reversibility in FEV_1 (L) / FEV_1 pre-salbutamol intake);

4.4.5 CAT and SGRQ

The CAT total score at Visit 1 and Visit 2 and the SGRQ total score and domain scores at Visit 2 (see section 4.7.2.12 for further details on calculation of the SGRQ scores) will be summarised by treatment group and overall using the ITT population. T14.1.9

4.4.6 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 (see Section 4.1.15 for definition of the run-in period and refer Section 4.7.2.15 for calculation) will be summarised by treatment group and overall using the ITT population. T14.1.10

4.4.7 Medical/Surgical 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 and ITT populations. The same summary will be also presented stratifying as detailed in Section 4.1.5. T14.1.11.1, T14.1.11.2, T14.1.11.3, T14.1.12.1, T14.1.12.2, T14.1.12.3

Notes:

- Medical/surgical history and concomitant diseases will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. There will be no update of dictionary during study conduct;
- 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.

4.4.8 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 population 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 PT. Post-study medications will only be presented in a listing. T14.1.13.1,-T14.1.13.7

The medications will be classified according to the following rules:

- previous medication: start date < date of start of randomised treatment period and 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-study 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 4.13.

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 common name and the associated Preferred Names considered in the analyses are summarised in APPENDIX II: COMMON NAME AND THE ASSOCIATED PREFERRED NAMES.

The following tables will be provided:

- previous medications and medications maintained during the randomised treatment period:
    - COPD medications including medications for COPD exacerbation;
    - non-COPD medications;
- concomitant medications:
    - COPD medications not including medications for COPD exacerbation;
    - medications for COPD exacerbation;
    - non-COPD medications.

It should be noted that, based on the above definitions, concomitant medications for COPD exacerbations may not include medications that started on or after the date of completion/discontinuation for an exacerbation with onset during the study period.

The rules to identify COPD medications (administered for COPD exacerbations and for other reasons) will be agreed during the BDRMs. The following rules are currently proposed for selecting medications (these may be amended during the BDRMs and any amendments will be fully documented in the DRP):

COPD Medications

Any medications satisfying the following condition (based on the data reviews performed) will be considered as COPD medications:

- indication containing 'COPD', 'CHRONIC OBSTRUCTIVE PULMONARY DISEASE';
- free text of CRF form "Prior and Concomitant Medications (CM)" to be checked for occurrences of COPD or similar texts (e.g., C.O.P.D.).

Medications for COPD Exacerbations

Any medications with an indication = 'COPD exacerbation during the study' will be considered as medications for COPD exacerbations.

Medications taken for COPD exacerbation during the study period will be associated to the number of the corresponding exacerbation based on the information provided in the prior and concomitant medications form of the eCRF. Medications with this information not available will be evaluated during the BDRMs in order to define the appropriate association.

Notes:

- Medications are coded using the World Health Organisation (WHO) Drug Dictionary, version June 2016. There will be no update of dictionary during study conduct;
- If a patient has multiple occurrences of a medication, the patient is presented only once in the respective patient count.

4.4.9 Procedures

Previous procedures, procedures maintained during the randomised treatment period, concomitant procedures will be summarised by treatment group and overall for the ITT population through frequency distributions and percentages by SOC and PT. Post-study procedures will only be presented in a listing. T14.1.14.1, T14.1.14.2, T14.1.14.3

The procedures will be classified according to the following rules:

- previous procedures: start date < date of start of randomised treatment period and 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-study procedures: start date ≥ date of end of randomised treatment period.

Notes:

- Procedures are coded using MedDRA version 19.0. There will be no update of dictionary during study conduct.

4.4.10 Vital Signs at Visit 1 and at Visit 2 Pre-dose

Systolic and diastolic blood pressure assessed at Visit 1 and pre-dose at Visit 2 will be summarised by treatment group and overall using the Safety population. T14.1.15

4.4.11 12-lead ECG at Visit 1 and Visit 2 Pre-dose

The number and percentage of patients with a pacemaker inserted before study entry and inserted during study will be presented. A patient will be classed as having a pacemaker according to the rule defined in section 4.1.12. T14.1.16.1, T14.1.16.2

HR, QTcF, PR and QRS obtained at Visit 1 and the average HR, QTcF, PR and QRS obtained in the triplicate 12-lead ECG at Visit 2 pre-dose will be summarised by treatment group and overall using the Safety population.

The number and percentage of patients with the following abnormalities will be presented by treatment group and overall using the Safety population:

- Atrial Fibrillation[S] (considering both "Atrial fibrillation" and "Possible atrial fibrillation");
- Atrial Flutter[S] (considering both "Atrial flutter" and "Possible atrial flutter");
- Ectopic Supraventricular Rhythm[S] (considering: "Premature atrial complex(es), conducted or non-conducted", "Premature atrial complex(es), conducted or non-conducted, in a bigeminy pattern", "Premature atrial complex(es), conducted or non-conducted, in a trigeminy pattern"," Premature atrial complex(es), conducted or non-conducted, couplets", "Run of premature atrial complex(es)", "Ectopic atrial rhythm", "Supraventricular rhythm", "Atrial tachycardia", "Possible atrial tachycardia", "Other supraventricular tachycardia including narrow QRS tachycardia", "Possible other supraventricular tachycardia including narrow QRS tachycardia", "Junctional premature complexes", "Possible junctional premature complexes", "Junctional premature complexes, in a bigeminy pattern", "Junctional premature complexes, in a trigeminy pattern", "Junctional premature complexes, couplets", "Junctional tachycardia", "Possible junctional tachycardia", "Junctional rhythm", "Possible junctional rhythm", Wandering atrial pacemaker (see P wave axis));
- Sinus Pauses[R] (considering both "Sinus pause or sino-atrial block (> 3 seconds) ", "Possible sinus pause or sino-atrial block (> 3 seconds)");
- Non-sustained Ventricular Tachycardia[V] (considering both "Non-sustained ventricular tachycardia" and "Non-sustained ventricular tachycardia, polymorphic");
- 2:1 AV Block[C] (considering both "2:1 AV block" and "Possible 2:1 AV block");
- AV Mobitz II[C] (considering both "2nd degree AV block, Mobitz 2" and "Possible 2nd degree AV block, Mobitz 2");
- Complete Heart Block[C] (considering both "3rd degree AV block" and "Possible 3rd degree AV block");
- Left Bundle Branch Block [I] (considering both "Complete left bundle branch block" and "Possible complete left bundle branch block");
- Right Bundle Branch Block [I] (considering: "Incomplete right bundle branch block"", "Possible incomplete right bundle branch block", "Complete right bundle branch block", "Possible complete right bundle branch block").

[S] Supraventricular Arrhythmias evaluation; [R] Rhythm evaluation; [V] Ventricular Arrhythmias evaluation; [C] AV Conduction evaluation; [I] Intraventricular Conduction evaluation.

A final confirmation of ECG abnormalities to be excluded from the statistical analysis will be made at the BDRM.

For the triplicate 12-lead ECG at Visit 2, all the abnormalities identified in the three measurements will be jointly considered in the analysis.

4.5 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.

For patients from South Korea, a different scheme of treatment administration will be applied to comply with regulatory requests. When the treatment kits are dispensed (Visit 2/Visit 4), the patient will be instructed to use the yellow and the blue pMDI + the yellow and the blue Turbuhaler® marked "1" during the first six weeks and the yellow and the blue pMDI + the yellow and the blue Turbuhaler® marked "2" during the last 6 weeks of the 12-week period.

Table 2: Schedule of treatment administration

China/ Taiwan	Korea
Twice a day: 4 inhalation in morning (yellow) / 4 inhalation in evening (blue)	**Twice a day:** 4 inhalation in morning (yellow) / 4 inhalation in evening (blue)
In the morning / evening: - 1 from yellow / blue label pMDI number 1 - 1 from yellow / blue label pMDI number 2 - 1 from yellow / blue label Turbuhaler® number 1 - 1 from yellow / blue label Turbuhaler® number 2	**In the morning / evening**: - 2 from yellow / blue label pMDI number 1 - 2 from yellow / blue label Turbuhaler ® number 1 **6 weeks later:** - 2 from yellow / blue label pMDI number 2 - 2 from yellow / blue label Turbuhaler® number 2

4.5.1 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 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 4.1.15).

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 doses 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 BID).

Descriptive summaries of treatment compliance (%) will be presented by treatment group for the run-in period using the ITT population. An additional summary displaying the number and percentage of patients in the following categories will also be presented by treatment group: T14.1.17.1

- [0%-10%];
- (10%-20%];
- (20%-30%];
- (30%-40%];
- (40%-50%];
- (50%-60%];
- (60%-70%];
- (70%-80%];
- (80%-90%];
- (90%-100%];
- (100%-110%];
- (110%-120%];
- (120%-130%];
- (130%-140%];
- >140%.

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

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

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 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 doses = Extent of exposure (days) * 8 (4 inhalations BID, considering 2 inhalation BID for CHF 5993 pMDI and 2 inhalation BID for Budesonide/formoterol).

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 (2 inhalations for each study medication) as study medication 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) * 4 + 4.

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

- # scheduled inhalations = 4 (2 inhalations for each study medication).

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 population. An additional summary displaying the number and percentage of patients in the following categories will also be presented by treatment group: T14.1.17.2

- [0%-10%];
- (10%-20%];
- (20%-30%];
- (30%-40%];
- (40%-50%];
- (50%-60%];
- (60%-70%];
- (70%-80%];
- (80%-90%];
- (90%-100%];
- (100%-110%];
- (110%-120%];
- (120%-130%];
- (130%-140%];
- >140%.

In addition, treatment compliance during the randomised treatment period will also be presented for the following categories: <75%, ≥75% and ≤125%, >125%.

4.5.3 Inter-Visit Periods

Inter-visit period visit i - visit i+1 ($2 \leq i \leq 5$)	
Date of start of the period	Date of end the period
• If i=2 then date of start = date of first randomised study medication intake. • Else date of start = date of visit i. Note: we are assuming date of first randomised study medication intake < date of Visit 3.	• If visit i is NOT the last clinic visit performed before the last randomised study medication intake then date of end = date of visit i+1 – 1 day (i.e., the day before visit i+1). • Else date of end = date of last randomised study medication intake. This includes the case date of last randomised study medication intake = date of Visit 6.

Data recorded from the date of start of the period to the date of end of the period will be considered as data of the inter-visit period.

Treatment exposure (days) during each inter-visit period is calculated as: date of end of the period – date of start of the period + 1.

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 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) * 4 (2 inhalations BID).

If the last day considered in the formula is the date of Visit 6 (date of last randomised study medication intake = Date of Visit 6), the number of scheduled puffs on this day will be 2 (2 inhalations) as study medication will be administered only in the morning. Therefore, the total number of scheduled puffs will be:

- [Extent of exposure (days) - 1] * 4 + 2.

For patients with date of discontinuation = date of Visit 2, then for the inter-visit period Visit 2 – Visit 3:

- # scheduled doses = 2 (2 inhalations).

Descriptive summaries of treatment compliance will be presented by treatment group for each inter-visit period using the ITT population. T14.1.17.3

4.6 Diary Compliance

Compliance to the use of diaries (run-in and randomised treatment periods) will be summarised using the ITT population, considering only the information on run-in/study medication and rescue medication (i.e. leaving out from the evaluation the COPD symptoms scores, that are just an additional information for the Investigator to check the health status of the patient during the treatment periods, and will not be analysed).

4.6.1 Run-in Period

A day is considered “with data recorded” when at least one of the following fields has been filled-up: number of run-in medication puffs in the morning, number of run-in medication puffs in the evening, number of rescue medication puffs in the day.

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

- Compliance during the run-in period (%) = [Total number of days in the run-in period with data recorded in the diaries / (Date of start of randomised treatment period – Date of Visit 1)]*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: T14.1.18.1

- [0%-10%];
- (10%-20%];
- (20%-30%];
- (30%-40%];
- (40%-50%];
- (50%-60%];
- (60%-70%];
- (70%-80%];
- (80%-90%];
- (90%-100%].

4.6.2 Randomised Treatment Period

A day is considered "with data recorded" when at least one of the following fields has been filled-up: number of yellow label pMDI number 1/2 puffs, number of yellow label Turbuhaler® number 1/2 inhalations, number of blue label pMDI number 1/2 puffs, number of blue label Turbuhaler® number 1/2 inhalations, number of rescue medication puffs in the day.

If date of end of randomised treatment period is the day of a clinic visit and no data are recorded in the diaries for this day, the following formula will be used:

- Compliance during the randomised treatment period (%) = [Total number of days in the randomised treatment period with data recorded in the diaries / (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 days in the randomised treatment period with data recorded in the diaries / (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 in the following categories of compliance will also be presented: T14.1.18.2

- [0%-10%];
- (10%-20%];
- (20%-30%];
- (30%-40%];
- (40%-50%];
- (50%-60%];
- (60%-70%];
- (70%-80%];
- (80%-90%];
- (90%-100%].

4.7 Efficacy Evaluation

The comparisons between CHF 5993 pMDI and Budesonide/formoterol will be conducted according to a hierarchical testing procedure. The primary efficacy variables will be analysed in the following order:

- change from baseline in pre-dose morning FEV_1 at Week 24 (see section 4.7.1.1);
- change from baseline to the 2-hour post-dose value of FEV_1 at Week 24 (see section 4.7.1.2);
- change from baseline in pre-dose morning FEV_1 at Week 24 in the Chinese population;
- change from baseline to the 2-hour post-dose value of FEV_1 at Week 24 in the Chinese population.

At each step of the procedure, no confirmatory claims will be made unless the superiority of CHF 5993 pMDI over Budesonide/formoterol will be demonstrated in all the preceding steps.

4.7.1 Primary Efficacy Variables

The primary efficacy variables are:

- Change from baseline in pre-dose morning FEV_1 at Week 24;
- Change from baseline to the 2-hour post-dose value of FEV_1 at Week 24.

4.7.1.1 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.

Pre-dose morning FEV_1 values at each visit will be summarised by treatment group using descriptive statistics. Changes from baseline (Visit 2, pre-dose) at each visit and to the average value will also be summarised by treatment group.

FEV_1 measurements excluded from statistical analysis will not be considered in the calculation of average pre-dose morning FEV_1 (see section 4.1.12).

The above summary will be performed using the ITT and PP populations. T14.2.1.1.x, T14.2.1.2.x

Change from baseline (Visit 2, pre-dose) in pre-dose morning FEV_1 will be analysed using a linear mixed model for repeated measures (MMRM) including treatment, visit, treatment by visit interaction, Country, number of COPD exacerbations in the previous year (1, >1), FEV_1 % of predicted normal value at baseline (<30%, ≥30%) and smoking status (ex-smoker, current smoker) at screening 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. In case of convergence issues, alternative covariance structures will be considered. This analysis will be performed using MIXED procedure in SAS. An example for SAS-code is given in Section □.

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 and overall will be estimated by the model and presented.

Superiority of CHF 5993 pMDI over Budesonide/formoterol will be demonstrated by a statistically significant difference between treatments at Week 24 (see Section 4.2 for p-value boundaries) favouring CHF 5993 pMDI.

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

A figure with adjusted mean change from baseline at each visit by treatment group derived from the linear MMRM will also be provided. F14.2.1.x

The analysis of pre-dose morning FEV_1 based on the linear MMRM will be also presented on the ITT population stratifying as detailed in Section 4.1.5 (Note: both ITT and PP population will be considered for the analyses of pre-dose morning FEV_1 conducted stratifying by country, and also summary of pre-dose morning FEV_1 will be provided for this stratification). The severity of airflow limitation will be excluded from the model in this stratified analysis. T14.2.1.3

The adjusted mean differences between treatments at Week 24 (Visit 6) and their 95% CIs estimated on the ITT and PP populations and in the stratified analyses will be graphically summarised in a forest plot (this means a total of one forest plot). F14.2.3

4.7.1.2 Change from Baseline in 2-hour Post-dose FEV_1 at Week 24 (Visit 6)

Since the analysis of change from baseline in 2-hour post-dose FEV_1 at Week 24 is based on the same statistical model used for the analysis of change from baseline in 2-hour post-dose FEV_1 at all the other clinic visits, details on this secondary efficacy variable is also provided in this section.

Two-hour post-dose FEV_1 values at each visit will be summarised by treatment group using descriptive statistics. Changes from baseline (Visit 2, pre-dose) at each visit will also be summarised by treatment group.

The above summary will be performed using the ITT and PP populations. T14.2.2.1.x
T14.2.2.2.x

The same statistical analysis as for pre-dose morning FEV_1 will be applied for 2-hour post-dose FEV_1 using the same fixed effects and covariates.

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 and presented.

Superiority of CHF 5993 pMDI over Budesonide/formoterol will be demonstrated by a statistically significant difference between treatments at Week 24 (see Section 4.2 for p-value boundaries) favouring CHF 5993 pMDI.

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

A figure with adjusted mean change from baseline at each visit by treatment group derived from the linear MMRM will also be provided. F14.2.2.x

The analysis of 2-hour post-dose FEV_1 based on the linear MMRM will be also presented on the ITT population stratifying as detailed in Section 4.1.5. (Note: both ITT and PP population will be considered for the analyses of 2-hour post-dose FEV_1 conducted stratifying by country, and also summary of 2-hour post-dose FEV_1 will be provided for this stratification). T14.2.2.3

The adjusted mean differences between treatments at Week 24 (Visit 6) and their 95% CIs estimated on the ITT and PP populations and in the stratified analyses will be graphically summarised in a forest plot (this means a total of one forest plot). F14.2.4

4.7.2 Secondary Efficacy Variables

The secondary efficacy variables are listed in Section 2.4, and will be analysed on the ITT population. All the secondary efficacy analysis will be also performed on the ITT population stratifying by Country (China, Korea and Taiwan).

4.7.2.1 Change from baseline in pre-dose and 2-hour post-dose FEV_1 at all the other clinic visits and over the entire treatment period

Since the analysis of the primary efficacy variable (change from baseline in pre-dose morning FEV_1 and in 2-hour post-dose 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 and in 2-hour post-dose at Visits 3, 4, 5, 6 and over the entire treatment period, details on the analysis are provided in section 4.7.1.1.

4.7.2.2 FEV_1 Response (Change from Baseline ≥ 100 ml) at Week 24

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 pre-dose morning FEV_1 value at the relevant time points will also be classified as non-responders.

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. T14.2.3.1.1, T14.2.3.1.2

FEV_1 response at Week 24 will be compared between treatment groups using a logistic model including treatment, Country, number of COPD exacerbations in the previous year, FEV_1 % of predicted normal value at baseline (<30%, ≥30%) and smoking status at screening 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 5993 pMDI vs. Budesonide/formoterol) with its 95% Wald CI and corresponding p-value will be estimated by the model.

The above summary/analyses will be repeated using the PP population. T14.2.3.2.1, T14.2.3.2.2

4.7.2.3 Change from Pre-dose to 2-hour Post-dose FEV_1 at all Clinic Visits

Changes from pre-dose morning FEV_1 values to 2-hour post-dose FEV_1 at each visit from Visit 3 onwards will be summarised by treatment group using descriptive statistics. T14.2.4.1, T14.2.4.2

At each clinic visit (from Visit 3 onwards), the change from pre-dose to the 2-hour post-dose value of FEV_1 will be analysed using an ANCOVA model including treatment, Country, number of COPD exacerbations in the previous year, FEV_1 % of predicted normal value at baseline (<30%, ≥30%) and smoking status at screening as fixed effects, and the pre-dose value at the visit as a covariate.

The number of patients considered in the model at each visit 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 and presented.

4.7.2.4 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 start date ≥ date of start of randomised treatment period and ≤ date of end of randomised treatment period will be considered in the analysis. COPD exacerbations with start date = date of start of randomised treatment period will be discussed case by case during the BDRM in order to evaluate if they should be classified as having occurred during the run-in or the randomised treatment period. The decisions taken will be documented in the DRR.

Two COPD exacerbations (irrespectively if the events were started before or after randomisation) 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 an exacerbation < 10 days);
- 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). Such cases will be discussed during the BDRM and the decisions taken will be documented in the DRR.

In case of at least one COPD exacerbation occurring before the randomisation and at least one COPD exacerbation occurring after randomisation are satisfying the rules above to be considered as single episode, then the resulting event will be considered as occurring before the randomisation (i.e. it will not be considered in the analyses of moderate and severe COPD exacerbations).

The above rule will not apply to 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 at least 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);
- the total duration of the treatment with systemic corticosteroids and/or antibiotics and the durations of treatment with systemic corticosteroids, treatment with antibiotics and hospitalisation will be summed. In case of overlapping treatments, each day will be counted only once;
- 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 at least 24 hours of stay (date/time of discharge – date/time of admission ≥ 24 hours) will be also considered as hospitalisations in the statistical analysis. Specific cases of COPD exacerbations requiring just access to the ER but no hospitalization were discussed during the data review meeting and final decision on their classification (moderate/severe) were reported in the DRR.

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

- it required hospitalisation (answer "*Yes*" to the question "*Hospitalisation needed?*" in the AE / COPD exacerbation form of the eCRF);
- it required emergency room admission (answer "*Yes*" to the question "*Emergency Room needed?*" in the AE / COPD exacerbation form of the eCRF) with at least 24

hours of stay (event to be considered as a hospitalisation, see the above paragraph) associated with systemic corticosteroids or antibiotics;

- it resulted in death (outcome = "*Fatal*" in the AE / COPD exacerbation form of the eCRF).

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 and the percentage of exacerbations and the exacerbation rate per patient per year will also be presented by treatment group for each of the following types of moderate/severe exacerbation: T14.2.5.1

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

T14.2.5.2

The number and the percentage of exacerbations treated with systemic corticosteroids and antibiotics, with systemic corticosteroids only and with antibiotics only and the number and percentage of exacerbations requiring hospitalisation will be presented by treatment group. The total duration of the treatment with systemic corticosteroids and/or antibiotics and the duration of the treatment with systemic corticosteroids and antibiotics, and of hospitalisation for moderate/severe COPD exacerbations will be summarised by treatment group using descriptive statistics and the following categorisations:

- total duration of the treatment: 1-15 days, 16-30 days, >30 days, Not Evaluable;
- systemic corticosteroids: 1-15 days, 16-30 days, >30 days, Not Evaluable;
- antibiotics: 1-30 days, >30 days, Not Evaluable.

A COPD exacerbation will be defined as treated with systemic corticosteroids if this treatment is recorded in the AE / COPD exacerbation form of the eCRF. The duration of the treatment will be evaluated considering the systemic corticosteroids (ATC code H02) associated with the exacerbation recorded in the Concomitant Medications form.

For each exacerbation treated with systemic corticosteroids, the duration of the treatment with systemic corticosteroids will be calculated by summing the duration of the associated courses. The duration of each course of systemic corticosteroids will be calculated using the following formula:

- Course duration (days) = stop date – start date +1

The days with overlapping courses will be counted only once. In case of at least one ongoing course or no associated systemic corticosteroids recorded in the concomitant medication form, the duration of the treatment with systemic corticosteroids will be classified as "Not Evaluable".

A COPD exacerbation will be defined as treated with antibiotics if this treatment is recorded in the AE / COPD exacerbation form of the eCRF. The duration of the treatment will be evaluated considering the antibiotic (ATC code J01) is associated with the exacerbation recorded in the Concomitant Medications form.

For each exacerbation treated with antibiotics, the duration of the treatment with antibiotics will be calculated as above described for systemic corticosteroids.

The total duration of the treatment with systemic corticosteroids and/or antibiotics will be calculated by summing the duration of the treatment with systemic corticosteroids and the duration of the treatment with antibiotics, counting only once the days with overlapping courses. If the duration of the treatment with systemic corticosteroids or the duration of the treatment with antibiotics will be classified as "Not Evaluable", also the corresponding total duration of the treatment with systemic corticosteroids and/or antibiotics will be classified as "Not Evaluable".

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.

T14.2.5.3

The number and the percentage of moderate/severe COPD exacerbations with the following etiologies will be presented by treatment group: Viral or Bacterial, Environmental Pollutants, Extrapulmonary Comorbidities, Concomitant Pulmonary Diseases, Other, Missing (if no etiology was recorded). A multiple etiology is possible: in this case the exacerbation will be counted in all the relevant categories (refer to the paragraph above when multiple etiologies are discussed).

Note: if "Other" category has been selected, but the Investigator did not provide any additional specification, then the record will be counted in the "Missing" category.

T14.2.5.4

The number of moderate and severe COPD exacerbations during the treatment period will be analysed using a negative binomial model including treatment, Country, number of COPD exacerbations in the previous year (1 or >1), FEV_1 % of predicted normal value at baseline (<30%, ≥30%) and smoking status at screening 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. An example for SAS-code is provided in Section □.

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).

The above summaries/analysis will be performed on the ITT population.

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.

4.7.2.5 Time to First Moderate / Severe COPD Exacerbation

Regarding the COPD exacerbations to be considered in the analysis and the COPD exacerbations to be considered as a single episode, see section 4.7.2.4.

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)/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]/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: T14.2.6.1.1, T14.2.6.1.2

- [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 75^{th}, 50^{th} and 25^{th} percentiles.

A Kaplan-Meier plot will also be presented. F14.2.5

The time to first moderate/severe COPD exacerbation will be analysed using a Cox proportional hazards model including treatment, Country, number of COPD exacerbations in the previous year, FEV_1 % of predicted normal value at baseline (<30%, ≥30%) and smoking status at screening 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 5993 pMDI vs. Budesonide/formoterol) will be presented as a hazard ratio with the associated 95% Wald CI and p-value.

4.7.2.6 Change from Baseline in Pre-dose Morning FVC at all Clinic Visits and over the entire treatment period

Pre-dose morning FVC values will be summarised at each visit by treatment group using descriptive statistics. Changes from baseline (Visit 2, pre-dose) will also be summarised at each post-baseline visit by treatment group. T14.2.7.1, T14.2.7.2

Changes from baseline in pre-dose morning FVC values at Visits 3, 4, 5, 6 and over the entire treatment period will be analysed using the same model as changes from baseline in pre-dose morning FEV_1 values (see section 4.7.1.1). Baseline FVC will be included as a covariate rather than baseline FEV_1.

4.7.2.7 Change from Baseline in 2-hour Post-dose FVC at all Clinic Visits and over the entire treatment period

Two-hour post-dose FVC values will be summarised at each visit by treatment group using descriptive statistics. Changes from baseline (Visit 2, pre-dose) will also be summarised at each post-baseline visit by treatment group. T14.2.8.1, T14.2.8.2

Changes from baseline in 2-hour post-dose FVC values at Visits 2, 3, 4, 5, 6 and over the entire treatment period will be analysed using the same model as changes from baseline in 2-hour post-dose FEV_1 values (see section 4.7.1.2). Baseline FVC will be included as a covariate rather than baseline FEV_1.

4.7.2.8 Change from Pre-dose to 2-hour Post-dose FVC at all Clinic Visits

Changes from pre-dose morning FVC values to 2-hour post-dose FVC at each visit from Visit 3 onwards will be summarised by treatment group using descriptive statistics. T14.2.9.1, T14.2.9.2

At each clinic visit (from Visit 3 onwards), the change from pre-dose to the 2-hour post-dose value of FVC will be analysed using an ANCOVA model including treatment, Country, number of COPD exacerbations in the previous year, FEV_1 % of predicted normal value at baseline (<30%, ≥30%) and smoking status at screening as fixed effects, and the pre-dose value at the visit as a covariate.

4.7.2.9 Pre-dose FEV_1/FVC at all Clinic Visits

Pre-dose FEV_1/FVC at each visit will be summarised by treatment group using descriptive statistics. T14.2.10

4.7.2.10 Change from Baseline in Pre-dose Morning Forced Expiratory Flow ($FEF_{25-75\%}$) at all Clinic Visits and over the entire treatment period

$FEF_{25-75\%}$ values will be summarised at each visit by treatment group using descriptive statistics. Changes from baseline (Visit 2, pre-dose) will also be summarised at each post-baseline visit by treatment group. T14.2.11.1, T14.2.11.2

Changes from baseline in pre-dose $FEF_{25-75\%}$ values at Visits 3, 4, 5, 6 and over the entire treatment period will be analysed using the same model as changes from baseline in pre-dose

morning FEV_1 values (see section 4.7.1.1). Baseline $FEF_{25-75\%}$ will be included as a covariate rather than baseline FEV_1.

4.7.2.11 Change from Baseline in Pre-dose Morning IC at all Clinic Visits and over the entire treatment period

Pre-dose morning IC values will be summarised at each visit by treatment group using descriptive statistics. Changes from baseline (Visit 2, pre-dose) will also be summarised at each post-baseline visit by treatment group. T14.2.12.1, T14.2.12.2

Changes from baseline in pre-dose morning IC values at Visits 3, 4, 5, 6 and over the entire treatment period will be analysed using the same model as changes from baseline in pre-dose morning FEV_1 values (see section 4.7.1.1). Baseline IC will be included as a covariate rather than baseline FEV_1.

4.7.2.12 Change from Baseline in the SGRQ Total Score and Domain Scores at all Clinic Visits and over the entire treatment period

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 4.13.

Weights of each item and other details for calculation are reported in APPENDIX I: ST. GEORGE'S RESPIRATORY QUESTIONNAIRE.

SGRQ total and domain (symptoms, impacts and activity) scores will be summarised at each visit by treatment group using descriptive statistics. Changes from baseline (Visit 2) will also be summarised at each post-baseline visit by treatment group. T14.2.13.1, T14.2.13.2

Changes from baseline in SGRQ total and domain (symptoms, impacts and activity) scores at Visits 3, 4, 5, 6 and over the entire treatment period will be analysed using the same model as for change from baseline in pre-dose morning FEV_1 (see section 4.7.1.1). Baseline total/domain scores will be included as a covariate rather than baseline FEV_1.

A figure with adjusted mean change from baseline at each visit by treatment group derived from the linear MMRM will also be provided for total score. F14.2.6.1, F14.2.6.2

4.7.2.13 SGRQ Response at Week 24

SGRQ response is defined as a change from baseline in total score ≤ -4. If the change from baseline is > -4 the patient is classified as a non-responder in terms of SGRQ. Patients with missing SGRQ total score at the relevant time points will also be classified as non-responders.

The summary/analysis performed for the FEV_1 response at Week 24 (see section 4.7.2.2) will be repeated for the SGRQ response. Baseline total score will be included as a covariate rather than baseline FEV_1. T14.2.14.1, T14.2.14.2

4.7.2.14 Changes from Baseline in COPD Assessment Test (CAT) at all Clinical Visits and over the entire treatment period

CAT total score will be summarised at each visit by treatment group using descriptive statistics. Changes from baseline (Visit 2) will also be summarised at each post-baseline visit by treatment group. T14.2.15.1, T14.2.15.2

Changes from baseline in CAT total score at Visits 3, 4, 5, 6 and over the entire treatment period will be analysed using the same model as for change from baseline in pre-dose morning FEV_1 (see section 4.7.1.1). Baseline CAT total score will be included as a covariate rather than baseline FEV_1.

4.7.2.15 Change from Baseline to each Inter-Visit Period and to the Entire Randomised Treatment Period in the Percentage of Days without Intake of Rescue Medication

The percentage of days without intake of rescue medications will be evaluated on the basis of the information recorded daily by the patient on the diaries. Please refer to Section 4.1.15 for definition of study periods.

The possible entries in the diary and corresponding categories for the intake of rescue medication and the corresponding number of puffs are summarised in the table below:

Diary: "Rescue medication, Salbutamol pMDI"				
Diary field "No inhalation"	Diary field "Yes"	Diary field "Number of inhalations"	Intake of rescue medication	Number of puffs
Any entry	Any entry	0	No	0
Ticked	Not ticked	Not filled	No	Missing data
Not ticked	Not ticked	Not filled	Missing data	Missing data
Ticked	Ticked	Not filled	Discrepant data	Missing data
Ticked	Any entry	>0	Discrepant data	Discrepant data

Not ticked Not ticked	Ticked Any entry	Not filled >0	Yes Yes	Missing data >0

During blinded dry-run 1, performed in April 2018, issues identified in the completion of paper diary. That is why the dates entered by patients in the paper diaries will be disregarded. Dates will be programmatically created based on dates available between visits, e.g. taking the date of visit 3 as start until the day before visit 4. This change will be applied to the data on SDTM level. An example is given below:

Diary record	# of puffs	Date included in the diary	Date to be included in the SDTM
1	2	03JAN2018	01JAN2018
2	2		02JAN2018
3	2	04JAN2018	03JAN2018
4		05JAN2018	
5	2		05JAN2018
6	2	07JAN2018	06JAN2018
7	2	08JAN2018	07JAN2018
8	3	01JAN2018	08JAN2018
9	4	09JAN2018	09JAN2018
10			
11	2	11JAN2018	11JAN2018
12	1	12JAN2018	12JAN2018
13			
…			

As a result, where the number of inhalations (puffs) is recorded, the record will be transferred into SDTM, regardless the date entered in the paper diary (e.g. records 1, 2, 3 will be transferred). If the number of inhalations (puff) is missing, the record will not be transferred into SDTM, but the diary record considered in the newly created date in SDTM (e.g. records 4, 10 and 13 will not be transferred).

Any diary data beyond date of Visit 6 / Early Termination visit will be discarded from analysis.

In case of multiple diary data for the same day, the last recorded observation will be considered for analysis purposes.

The same approach will be used for entries about the use of rescue medication as well.

For the computation of the percentage of days without intake of rescue medication, days without intake of rescue medication will be counted in the numerator (excluding days with missing or discrepant data regarding the intake of rescue medication), whereas days with available consistent data will be counted in the denominator (excluding days with missing or discrepant data regarding the intake of rescue medication).

Run-in Period

On a per patient basis, the percentage of days in the run-in period will be calculated using the following formula:

- % of days without rescue medication (run-in period) = (Number of days without rescue medication during the run-in period / Number of days with consistent data recorded during the run-in period)*100.

Inter-Visit Period

Inter-visit period visit i - visit i+1 ($2 \leq i \leq 5$)	
Date of start of the period	Date of end the period
• If i=2 then date of start = date of start of randomised treatment period. • Else date of start = date of visit i.	• If visit i is NOT the last clinic visit performed before completion/ discontinuation then date of end = date of visit i+1 – 1 day (i.e., the day before visit i+1). • Else date of end = date of end of randomised treatment period. This includes the case date of visit i = date of completion/discontinuation.

On a per patient basis, the percentage of days in each inter-visit period during the randomised treatment period will be calculated using the following formula:

- % of days without rescue medication (inter-visit period) = (Number of days without rescue medication during the inter-visit period / Number of days with consistent data recorded during the inter-visit period)*100.

Randomised Treatment Period

On a per patient basis, the percentage of days in the entire randomised treatment period will be calculated using the following formula:

- % of days without rescue medication (randomised treatment period) = (Number of days without rescue medication during the randomised treatment period / Number of days with consistent data recorded during the randomised treatment period)*100.

Data recorded in the evening of the day of the Visit 2 are partly based on a pre-dose period, but they will be considered in the calculation regarding the randomised treatment period.

The percentage of days without intake of rescue medication will be summarised for the run-in period, each inter-visit period and the entire randomised treatment period using descriptive statistics by treatment group. The change from baseline (run-in period) to each inter-visit period and to the entire randomised treatment period will also be summarised. T14.2.16.1, T14.2.16.2

Change from baseline (run-in period) to each inter-visit period in the percentage of days without intake of rescue medication will be analysed using a similar model as for change from baseline in pre-dose morning FEV_1 (see section 4.7.1.1). The inter-visit period will be considered instead of visit in the model and baseline percentage of days without intake of rescue medication scores will be included as a covariate rather than baseline FEV_1. Change from baseline to the entire treatment period will be also analysed using this model, by assigning to each inter-visit period a weight proportional to its expected duration.

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

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

4.7.2.16 Change from Baseline to each Inter-Visit Period and to the Entire Randomised Treatment Period in the Average Use of Rescue Medication (Number of Puffs/Day)

Use of rescue medications will be evaluated on the basis of the information recorded daily by the patient on the diaries.

The same evaluations on diary data for the percentage of days without rescue medication use will be implemented also for the average use of rescue medications.

Average use of rescue medication will be evaluated as number of puffs per day. In formula, the average will be calculated as

Average use of rescue medication (run-in period, inter-visit period, randomised treatment period) = (total number of puffs during the period / Number of days with consistent data with use of rescue medication during the period).

See section 4.1.15 for the definition if run-in, inter-visit and entire randomised treatment periods.

On each period, the average use of rescue medication will be calculated as the mean number of puffs per day based on the data recorded, excluding days with discrepant data entries. T14.2.17.1, T14.2.17.2

The summary/analysis performed for the percentage of days without intake of rescue medication will be performed for the average use of rescue medication.

4.8 Health Economic Variables

4.8.1 EQ-5D-3L

The EQ-5D-3L consists of the EQ-5D descriptive system and the EQ VAS. The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain / discomfort and anxiety / depression. Each dimension has 3 levels: no problems, some problems, extreme problems. A unique health state is defined by combining 1 level from each of the 5 dimensions. There are 243 possible health states defined in this way. Each state is referred to in terms of a 5-digit code. No health state value will be calculated if any of the dimensions is missing.

For example, if a patient provides the following responses: Mobility=No problems, Self-care=No problems, Usual Activities=Moderate problems, Pain/Discomfort=Moderate problems, Anxiety/Depression=Extreme problems, his response sequence is 11223. The 243 theoretical possible sequences can then be mapped to an index value to provide a summary across all dimensions. For the calculation of the index value, the UK value set based on Time Trade-Off method will be used [3]. The scoring algorithm is as follows:

Full health (11111) =	1.000
At least one domain at 2 or 3 (N2):	-0.081
At least one domain at 3 (N3):	-0.269
Mobility level 1:	0
Mobility level 2:	-0.069
Mobility level 3:	-0.314
Self-care level 1:	0
Self-care level 2:	-0.104
Self-care level 3:	-0.214
Usual activities 1:	0
Usual activities 2:	-0.036
Usual activities 3:	-0.094
Pain/discomfort 1:	0
Pain/discomfort 2:	-0.123
Pain/discomfort 3:	-0.386
Anxiety/depression 1:	0
Anxiety/depression 2:	-0.071
Anxiety depression 3:	-0.236

The index for the patient with example sequence 11223 = 0.255, calculated as follows:

Full health =1

Minus N2: -0.081
Minus N3: -0.269
Minus mobility level 1: 0
Minus self-care level 1: 0
Minus usual activities level 2: -0.036
Minus pain/discomfort level 2: -0.123
Minus anxiety/depression level 3: -0.236

where level 1 corresponds to no problems, level 2 to some problems and level 3 to extreme problems.

The EQ VAS records the patient's self-rated health on a vertical, visual analogue scale where the endpoints are 'Worst imaginable health state' (0) and 'Best imaginable health state' (100).

The index values and VAS scores will be summarised by treatment group and visit (1st and 3rd quartiles will be included in addition to the standard summary statistics). T14.2.18.1

4.8.2 Other Health Economic Data

For each patient, the total count during the randomised treatment period will be calculated by summing the values recorded at all available visits from Visit 3 onwards for the following variables:

- Number of hospital admissions due to COPD and other causes;

- Number of hospital days due to COPD and other causes;
- Number of emergency room visits due to COPD and other causes;
- Number of ambulance rides to hospital due to COPD and other causes;
- Number of days in ICU due to COPD and other causes;
- Number of unscheduled contacts due to COPD:
  - family practitioner;
  - specialist outpatients setting;
  - specialist hospital outpatients setting;
- Number of days with professional home assistance due to COPD;
- Number of days with family caregivers due to COPD;
- Number of days with of oxygen therapy use due to COPD;
- Unplanned diagnostic or instrumental tests performed due to COPD;
- Lost productivity due to COPD (sick leave days from work).

T14.2.18.2

A descriptive summary of the total number of events/days will be presented by treatment group. Only employed patients (i.e., with professional status = employed full time or employed part time for the whole study duration) will be considered when summarising the total number of sick leave days from work.

Of note, the descriptive summary based on totals does not consider the differences in the follow-up duration of the patients and the potential impact of missing data.

T14.2.18.3

The patient professional status at Visit 2 and the anticipated retirements due to inability or sickness occurred during the study will be summarised. Anticipated retirements due to inability or sickness recorded after Visit 2 on patients employed (full-time or part-time) at Visit 2 will be considered as having occurred during the study.

4.8.3 Mortality

The information on mortality will be provided in the analysis of AEs (treatment emergent AEs leading to death).

4.9 Safety Analysis

All safety variables will be summarised using the safety population and will be presented also stratifying by Country (China, Korea and Taiwan).

The safety variables are:

- AEs and ADRs;
- Vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP]);
- 12-lead ECG parameters: HR, QTcF, PR and QRS;

- Standard haematology and blood chemistry.

Exposure to randomised study medication will be also summarised.

4.9.1 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 2-week categories of extent of exposure will also be presented:

- [0-2);
- [2-4);
- [4-6);
- [6-8);
- [8-10);
- [10-12);
- [12-14);
- [14-16);
- [16-18);
- [18-20);
- [20-22);
- [22-24);
- ≥24.

Descriptive statistics of extent of exposure in days and weeks will be provided by treatment group. T14.3.1.1.1, T14.3.1.1.2

Please note that Week 24 (Visit 6) defines the end of treatment period. A morning dose is scheduled at Visit 6 which defines the last administration of study medication.

4.9.2 Adverse Events

COPD exacerbations will be reported in the same eCRF form as for AEs and identified through by "*Yes*" to the question "*Is this AE an COPD exacerbation*". Therefore, all COPD exacerbations are analysed as AEs and included in the analysis of AEs (tables and listings).

An AE will be classified as pre-Treatment AE if it starts before the first randomised study medication intake (AE onset date < date of first randomised study medication intake).

An AE will be classified as a treatment emergent AE (TEAE) if the AE onset date is following the constraint: date of first randomised study medication intake ≤ AE onset date ≤ date of completion/discontinuation.

An AE will be classified as a post-study AE if the AE onset date > date of completion/discontinuation.

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

A serious ADR is an SAE classified as related to the study medication.

A severe AE is an AE with severe intensity.

An AE leading to discontinuation from randomised study medication 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-study 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 run-in study medication intake (if AE onset date is completely known);
    - missing (if AE onset date is incomplete or unknown).
- For TEAEs:
    - AE onset date - date of first randomised study medication intake +1 (if AE onset date is completely known);
    - missing (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);
- 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";
- missing (when the AE onset date is incomplete or unknown, or when the AE was resolved but with an incomplete or unknown end date, or when the AE onset date is > date of completion/discontinuation and the AE is not resolved).

The number of days from completion/discontinuation to onset of a post-study AE will be calculated as follows:

- AE onset date – date of completion/discontinuation (if AE onset date is completely known);
- missing (if AE onset date is incomplete or unknown).

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

The number of treatment-emergent AEs, SAEs, ADRs, serious ADRs, severe AEs, AEs leading to discontinuation from randomised study medication and AEs leading to death, and the number and the percentage of patients experiencing treatment-emergent AEs, SAEs, ADRs, serious ADRs, severe AEs, AEs leading to discontinuation from randomised study medication and AEs leading to death will be summarised by treatment group. T14.3.1.2.x

AEs will be coded using the MedDRA dictionary (version 19.0) and not updated during study conduct. The SOCs and PTs will be used for tabulation. The number and percentage of patients with at least one AE and the number of AEs will be presented by SOC and PT by treatment group for treatment-emergent AEs, SAEs, ADRs, serious ADRs, severe AEs, AEs leading to discontinuation from randomised study medication and AEs leading to death. T14.3.1.3.x T14.3.1.4, T14.3.1.5, T14.3.1.6, T14.3.1.7, T14.3.1.8, T14.3.1.9,

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 ≥ 1% of patients in any treatment group) will be provided. PTs will be used for tabulation.

The number and percentage of patients with any treatment-emergent pneumonias, serious pneumonias, pneumonias related to study medication, serious pneumonias related to study medication, severe pneumonias, pneumonias leading to discontinuation, pneumonias leading to death will be presented by treatment group. The number of events will also be displayed. In addition, the number and percentage of patients and number of events will be displayed for each type of pneumonia (within each of the above categories). The following types of pneumonia will be included: community acquired pneumonia, nosocomial pneumonia, lobar pneumonia, bronchopneumonia and interstitial pneumonia. T14.3.1.10

Treatment emergent pneumonias will be also analysed in terms of rate per 1'000 patient per year. The follow-up time in years will be calculated using the following formula: T14.3.1.11

- Follow-up time (years) = [date of completion/discontinuation - date of first randomised study medication intake + 1] / 365.25.

The rate of treatment emergent pneumonia per 1000 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 events by the total follow-up time, multiplying the result by 1000).

The number and percentage of patients and number of events with each method of diagnosis (medical imaging, blood test, bronchoscopy, sputum analysis, other) and each potential cause (severe acute respiratory syndrome, chemical compounds, aspiration, dust, assisted/mechanical ventilation, trauma, pulmonary embolism, other) will also be presented by treatment group. T14.3.1.12

4.9.3 Vital Signs

SBP and DBP will be summarised by treatment group at each visit/time point from Visit 2 onwards by means of descriptive statistics. Changes from baseline (Visit 2, pre-dose) to each time point after the first study medication intake and from pre-dose to 10 min post-dose at each visit (from Visit 3 onwards) will also be summarised. 95% CIs for the mean changes from baseline/pre-dose will also be presented. T14.3.5.1, T14.3.5.2

4.9.4 12-lead ECG

12-lead ECGs will be performed prior to the bronchodilator administration at Visit 1 and prior to dosing and at 10 min post-dose at Visit 2, Visit 4 and Visit 6. The pre-dose ECG at Visit 2 will be performed in triplicate and all other ECGs will be single ECGs. For summaries and analyses, the average of the triplicate values at Visit 2, pre-dose will be used. The individual triplicate values will be listed.

For 12-lead ECG parameters (HR, QTcF, PR and QRS), the absolute values and the changes from baseline (Visit 2, pre-dose) at each time point after the first study medication intake, and the changes from pre-dose to 10 min post-dose at Visit 4 and Visit 6 will be summarised by treatment group. 95% CIs for the mean absolute values will also be presented. T14.3.6.1, T14.3.6.2.x, T14.3.6.3, T14.3.6.4,

The number and the percentage of patients with a

- QTcF >450 ms, >480 ms and >500 ms for males and QTcF >470 ms and >500 ms for females;
- change from baseline in QTcF >30 ms and >60 ms;
- only for post-dose time points: change from pre-dose at the same visit in QTcF >30 ms and >60 ms

at any time point after the first study drug intake will be presented by treatment group.

The number and percentage of patients with any ECG abnormalities as detailed in Section 4.4.11 at any time point after the first study drug intake will be presented by treatment group using the Safety population and stratifying as detailed in Section 4.1.5. T14.3.6.5

4.9.5 Laboratory Findings

The following laboratory parameters will be recorded at Visit 1 (Screening), Visit 4 (Week 12), Visit 5 (Week 18) and Visit 6 (Week 24):

Haematology:

Red blood cell (RBC) count, white blood cell (WBC) count and differential (basophils, eosinophils, lymphocytes, monocytes and neutrophils), total haemoglobin (Hb), haematocrit (Hct) and platelets count (PLT).

Biochemistry:

Creatinine, blood urea nitrogen (BUN), fasting serum glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GT), total bilirubin, alkaline phosphatase, sodium (Na), potassium (K), calcium (Ca), chloride (Cl) electrolytes, and albumin.

In addition, serum Beta-Human Chorionic Gonadotropin (β-HCG) is collected (only for females of childbearing potential) at Visit 1 and Visit 6 and a urine pregnancy test is performed at Visits 1 to 5.

Laboratory results at Visits 1, 4, 5 and 6 and changes from screening in laboratory results at Visits 4, 5 and 6 will be summarised by treatment group. 95% CIs for the mean changes will also be presented. T14.3.7.1, T14.3.7.3

Shift tables from screening to Visits 4, 5 and 6, with regard to normal range (low clinically significant [CS], low not clinically significant [NCS], normal, high NCS, high CS), will be presented by treatment group for each of the laboratory parameters. T14.3.7.2, T14.3.7.4

Pregnancy test results will be listed only.

4.9.6 Independent Data Monitoring Committee

An independent DMC will be appointed for this study. The DMC will be operating under full confidentiality and bound to take decisions as outlined below. No member of the DMC or the DMC itself will communicate any aspects other than what is detailed below. The DMC will have at least 3 members as follows:

- 2 independent physicians,
- an independent statistician.

A DMC Charter will detail the responsibilities of the DMC members, the amount of information expected to undergo DMC evaluation, the endpoints that will be assessed, and the level of evidence required to claim superiority. In the review of the unblinded results, focus will be given to:

a) the primary efficacy endpoints: change from baseline in pre-dose morning FEV_1 at Week 24 and change from baseline in 2-hour post-dose FEV_1 at Week 24 in the overall and Chinese populations;

b) patient's safety: treatment-emergent adverse events.

After review of the unblinded results the DMC will make a final recommendation. This recommendation can either be:

- to stop the recruitment. If the Sponsor will decide to follow this recommendation, then the interim analysis results will be disclosed to both PPD and Sponsor study teams;
- to continue the recruitment until the initial planned target number of patients, without disclosing the interim study results. In this case, final analysis will be conducted including all the patients.

Please refer to Section 4.2 for possible scenarios and borders for claiming superiority.

4.10 Other Data

All other data collected in the eCRF will be listed only.

4.11 Adjustment for Covariates

For all ANCOVA models, repeated measures models, Cox regression models, negative binomial models and logistic models the covariates, fixed effects and interactions are defined in the respective sections.

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 country, the country will not be included as a factor in the model).

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 (introduced by OM-Option in LSMEANS-Statement);

- effects of quantitative covariates set equal to their mean values in the group of patients analysed (introduced by AT MEANS-Option in LSMEANS-Statement).

4.11.1 Centre Effects

No centre effects will be investigated.

4.12 Protocol Deviations

Major protocol deviations may include wrong inclusions, poor compliance and non-permitted concomitant medications. Exact definition of major and minor protocol deviations will be discussed at the BDRMs and documented in the DRR.

The finalisation of protocol deviations and exclusions from the PP population will be made prior to the randomisation code being revealed.

Major and minor protocol deviations will be listed and summarised by treatment group using the ITT population (deviations affecting efficacy) (see section 4.3). Deviations will be classified according to the following categories:

- VIOLATION OF INCLUSION CRITERION;
- VIOLATION OF EXCLUSION CRITERION;
- NON ADEQUATE COMPLIANCE TO THE RUN-IN MEDICATION;
- NON ADEQUATE COMPLIANCE TO THE STUDY MEDICATION;
- TREATMENT ADMINISTRATION DEVIATION;
- NON PERMITTED MEDICATION;
- ASSESSMENT PERFORMED OUTSIDE THE ALLOWED TIME WINDOW;
- VISIT PERFORMED OUTSIDE THE ALLOWED TIME WINDOW;
- STUDY PROCEDURE DEVIATION;
- RANDOMISATION CODE BROKEN;
- WASH-OUT PERIOD NOT RESPECTED.

These categories may be amended, or other categories may be added, but any changes will be made prior to database lock and will be documented in the DRR.

In addition, it is anticipated that data may be excluded from the PP analysis on a by-visit basis.

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 measurement at Visit 2 is excluded. Regarding the calculation of average pre-dose morning FEV_1 in the PP analysis, see Section 4.7.1.1.

4.13 Handling of Missing Data

For the primary efficacy variables, linear MMRM will be used to handle missing data. Under the 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.

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.

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 documented COPD exacerbation, the following rules will be applied for the partial dates of last documented 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.

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

- Symptoms score: missing items ≤ 2;
- Activity score: missing items ≤ 4;
- Impacts score: missing items ≤ 6.

If at least one domain score will be missing, the total score will be considered as missing.

A minimum of 7 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.

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-study medication;
- previous medication.

Only COPD exacerbations with onset during the randomised treatment period (i.e., with onset date ≥ date of start of randomised treatment period and ≤ 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 and in the algorithm defined below for the calculation of the duration of the treatment of a COPD exacerbation with systemic corticosteroids and/or antibiotics.

In case of partial end date of COPD exacerbation due to missing day, the end of the event will be assumed as the last day of the month in the algorithm defined below for the calculation of the duration of the treatment of a COPD exacerbation with systemic corticosteroids and antibiotics.

In case of emergency room admission 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).

For the calculation of the duration of the treatment of a COPD exacerbation with systemic corticosteroids and antibiotics, the following rules will be applied (considering the date of start and stop of exacerbations before grouping the exacerbations to be considered as a single episode):

- in case of completely missing treatment start date, the exacerbation start date will be considered as the treatment start date;
- in case of partial treatment start date, the imputation will be performed according to the following algorithm:
  1. impute treatment start date considering the last day of the year/month;
  2. if treatment start date imputed according to step 1 ≤ exacerbation start date, then stop. Else go to step 3;
  3. impute treatment start date as max(treatment start date imputed considering the first day of the year/month, exacerbation start date).
- in case of completely missing treatment stop date, the exacerbation stop date will be considered as the treatment stop date. Of note, this rule will not be applied if the medication is recorded as ongoing, since in this case the duration of the treatment will be classified as "Not Evaluable" (see section 4.7.2.4);
- in case of partial treatment stop date, the imputation will be performed according to the following algorithm:
  1. impute treatment stop date considering the first day of the year/month;

2. if treatment stop date imputed according to step 1 ≥ exacerbation stop date, then stop. Else go to step 3;
3. impute treatment stop date as min(treatment stop date imputed considering the last day of the year/month, exacerbation stop date).

In the responder analyses, patients with missing data at the relevant time points will be considered as non-responders. Patients with missing baseline value 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 Data Review Report), it will be imputed as the overall mean baseline value (considering patients from both treatment groups with available baseline value in the relevant analysis population). This will allow the inclusion of all patients in the statistical analysis.

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:

1. treatment emergent;
2. post-study;
3. pre-treatment.

12-lead ECGs should be performed in triplicate at Visit 2 and in the analyses the average of the triplicate values will be used. If less than 3 measurements will be available, the average of the available measurements will be considered.

Other critical missing data, if any, will be discussed during the blind review of the data. Decisions will be fully documented in the DRR.

4.14 Deviations from SAP

Any deviations from the SAP will be described and justified in the final clinical study report.

4.15 Changes in the Conduct of the Study or Planned Analysis

- Parameter name MMEF was replaced by FEF25-75% to be in line with recent SDTM and spirometry data transfer specification. No other change implemented in the methodology of analysis other than the change in label.
- The airflow severity at baseline, measured by FEV1 % of predicted of normal, is not included in the statistical models as fixed effect given the current CSP (refer to Section 12.4.1 and 12.4.2 of the CSP). After blinded dry-run #1 the importance of the airflow severity at baseline on the FEV1 outcome was revisited and, considering that the study is stratified on country only, the adjustment of the statistical models by including the airflow severity as fixed effect is justified.

- A formal interim analysis was introduced with Protocol amendment #3 (#4 South Korea version). Details about interim analysis and DMC added (see Sections 4.2 and 4.9.6 for further details).
- Definition of the Safety and ITT population was slightly modified, in order to take into account the case of a patient who was randomised twice during the study in two different sites (see Sections 3.5.1, 3.5.2 and 3.5.4 for further details).

4.16 Algorithms/SAS Codes

The SAS codes below are given for SAS version 9.3. Prior to the DB lock and prior to the unblinding for the final analysis, the SAS version to be used for the final analysis will be agreed on, and all the SAS codes below will be re-checked based on this SAS version. The SAS version used for the final analysis will be specified in this SAP, including relevant version numbers of submodules, e.g. SAS/STAT. The variable names in the following codes may be different in the actual programs.

Tables that need 95% CIs within group for continuous variables:

```
DATA outdata;
    SET outname;
    LCL=mean-(TINV(0.975,n-1)*(std/SQRT(n)));
    UCL=mean+(TINV(0.975,n-1)*(std/SQRT(n)));
RUN;
```

Tables that require Kaplan-Meier estimates and log-rank test:

```
PROC LIFETEST data=dataset timelist=(0 4 12 18 24 EoS) alpha=.05 outsurv=estim reduceout;
    TIME time*event(0);
    STRATA tmt;
RUN;
```

Notes:

- Time represents the time to event or time to censoring;
- Event represents the censoring indicator (0 = censored);
- Tmt represents the treatment group;
- EoT should be replaced by the last time to event >24 weeks (if any).

Tables that require Cox proportional hazards model and 95% CIs of hazard ratios between treatments:

```
PROC PHREG data=dataset;
    CLASS tmt(REF='Budesonide/formoterol')
          country(REF='China')
          n_COPD_exac(REF='1')
          smoking(REF='Ex-Smoker')
          airflow_sev(REF='>=30%')
     / param=reference;
    MODEL time*event(0) = tmt country n_COPD_exac smoking airflow_sev
        / ties=exact type3(wald) RL=wald;
    HAZARDRATIO tmt / cl=wald diff=REF;
RUN;
```

Notes:

- Tmt represents the treatment group;
- Country represents the (pooled) Country;
- n_COPD_exac represents the number of COPD exacerbations in the last year (classified into 2 groups: 1 or >1);
- Smoking represents the smoking status at Screening;
- airflow_sev represents the FEV1% of predicted normal at baseline
- Time represents the time to event or time to censoring;
- Event represents the censoring indicator (0 = censored);
- Treatment order: 1 = CHF 5993 pMDI, 2 = Budesonide/formoterol;
- If the option ties=exact requires a considerable amount of computer resources, the Efron approximation will be used (ties=efron).

Tables that require logistic model, including 95% CIs of odds ratios:

```
PROC LOGISTIC data=dataset;
    CLASS tmt(REF='Budesonide/formoterol')
          country(REF='China')
          n_COPD_exac(REF='1')
          smoking(REF='Ex-Smoker')
          airflow_sev(REF='>=30%')
    / param=reference;
    MODEL response (EVENT='1') = tmt country n_COPD_exac smoking airflow_sev
baseline
        / expb clodds=wald;
RUN;
```

Notes:

- Response represents the binary variable (responder/non-responder) for each patient. We are assuming to model the probability of "response" (and not the probability of "no response");
- Tmt represents the treatment group;

- Country represents the (pooled) Country;
- n_COPD_exac represents the number of COPD exacerbations in the last year (classified into 2 groups: 1 or >1);
- Smoking represents the smoking status at Screening;
- airflow_sev represents the FEV1% of predicted normal at baseline
- Baseline represents the baseline FEV_1/SGRQ value for each patient;
- Treatment order: 1 = CHF 5993 pMDI, 2 = Budesonide/formoterol;

Calculation of adjusted means (least squares means):

The approach described below 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 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.

Example: analysis of change from baseline (Visit 2) at all visits (Visits 3 to 6) based on a mixed model for repeated measures including the effects of treatment, visit (categorical variable), treatment by visit interaction, baseline and another covariate. Visit 1 represents the screening visit.

Original dataset (X = available value, . = missing or invalid value):

Patient	Treatment	Covariate	Baseline	Visit	Change from baseline
1	CHF 5993 pMDI	X	X	1	.
1	CHF 5993 pMDI	X	X	2	.
1	CHF 5993 pMDI	X	X	3	X

1	CHF 5993 pMDI	X	X	4	X
1	CHF 5993 pMDI	X	X	5	X
1	CHF 5993 pMDI	X	X	6	X
2	Budesonide/formoterol	X	X	1	.
2	Budesonide/formoterol	X	X	2	.
2	Budesonide/formoterol	X	X	3	X
3	CHF 5993 pMDI	X	X	1	.
3	CHF 5993 pMDI	X	X	2	.
3	CHF 5993 pMDI	X	X	3	X
3	CHF 5993 pMDI	X	X	4	.
3	CHF 5993 pMDI	X	X	5	X
3	CHF 5993 pMDI	X	X	6	X
4	Budesonide/formoterol	X	X	1	.
4	Budesonide/formoterol	X	X	2	.
5	CHF 5993 pMDI	.	X	1	.
5	CHF 5993 pMDI	.	X	2	.
5	CHF 5993 pMDI	.	X	3	X

Step 1 (visits 1 and 2 not selected since they are pre-randomisation, patient 4 not selected due to missing post-randomisation measurements, patient 5 not selected due to missing covariate):

Patient	Treatment	Covariate	Baseline	Visit	Change from baseline
1	CHF 5993 pMDI	X	X	3	X
1	CHF 5993 pMDI	X	X	4	X
1	CHF 5993 pMDI	X	X	5	X
1	CHF 5993 pMDI	X	X	6	X
2	Budesonide/formoterol	X	X	3	X
3	CHF 5993 pMDI	X	X	3	X
3	CHF 5993 pMDI	X	X	4	.
3	CHF 5993 pMDI	X	X	5	X
3	CHF 5993 pMDI	X	X	6	X

Step 2 (added records in *italic*):

Patient	Treatment	Covariate	Baseline	Visit	Change from baseline
1	CHF 5993 pMDI	X	X	3	X
1	CHF 5993 pMDI	X	X	4	X
1	CHF 5993 pMDI	X	X	5	X
1	CHF 5993 pMDI	X	X	6	X
2	Budesonide/formoterol	X	X	3	X
2	*Budesonide/formoterol*	*X*	*X*	*4*	.
2	*Budesonide/formoterol*	*X*	*X*	*5*	.

2	*Budesonide/formoterol*	*X*	*X*	*6*	.
3	CHF 5993 pMDI	X	X	3	X
3	CHF 5993 pMDI	X	X	4	.
3	CHF 5993 pMDI	X	X	5	X
3	CHF 5993 pMDI	X	X	6	X

Tables that require negative binomial modelling, including 95% CIs of treatment ratios:

```
PROC GENMOD data = dataset;
    CLASS tmt(REF='Budesonide/formoterol')
          country(REF='China')
          n_COPD_exac(REF='1')
          smoking(REF='Ex-Smoker')
          airflow_sev(REF='>=30%');
    MODEL count = tmt country n_COPD_exac smoking airflow_sev
                  / offset=log_years dist=negbin link=log wald type3;
    LSMEANS tmt / om cl exp;
    ESTIMATE 'A vs B' tmt 1 -1 / exp;
RUN;
```

Notes:

- Count represents the total number of exacerbations for each patient;
- Tmt represents the treatment group;
- Country represents the (pooled) Country;
- n_COPD_exac represents the number of COPD exacerbations in the last year (classified into 2 groups: 1 or >1);
- Smoking represents the smoking status at Screening;
- airflow_sev represents the FEV1% of predicted normal at baseline
- log_years represents the logarithm of the follow-up time in years;
- Treatment order: 1 = CHF 5993 pMDI, 2 = Budesonide/formoterol.

Tables that require linear mixed model for repeated measures for spirometry (pre-dose), SGRQ and 95% CIs of differences between treatments:

```
PROC MIXED data = dataset;
    CLASS tmt visit country n_COPD_exac airflow_sev smoking patient;
    MODEL change = tmt visit tmt*visit country n_COPD_exac smoking airflow_sev baseline
                   baseline*visit
                  / ddfm=kr;
    REPEATED visit / subject=patient type=un;
    LSMEANS tmt 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,
        'A vs B: Week 24'  0 0 0 1 0 0 0 -1/ cl;
```

LSMESTIMATE tmt 'A vs B: Overall' 1 -1 / cl;
RUN;

Notes:

- Change represents the change from baseline to each visit of the variable;
- Tmt represents the treatment group;
- Visit represents the clinic visit;
- Country represents the (pooled) Country;
- 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 normal at baseline
- Smoking represents the smoking status at Screening;
- Baseline represents the baseline value of the variable;
- Patient represents the Patient Number;
- Treatment order: 1 = CHF 5993 pMDI, 2 = Budesonide/formoterol.
- the 'Overall' least squares means and contrasts will be estimated only for the change from baseline in pre-dose morning FEV_1.

Tables that require linear mixed model for repeated measures for post-dose spirometry and 95% CIs of differences between treatments:

```
PROC MIXED data = dataset;
    CLASS tmt visit country n_COPD_exac airflow_sev smoking patient;
    MODEL change = tmt visit tmt*visit country 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 0'    1 0 0 0 0 -1 0 0 0,
        'A vs B: Week 4'    0 1 0 0 0 0 -1 0 0 0,
        'A vs B: Week 12'  0 0 1 0 0 0 0 -1 0 0,
        'A vs B: Week 18'  0 0 0 1 0 0 0 0 -1 0,
        'A vs B: Week 24'  0 0 0 0 1 0 0 0 0 -1/ cl;
    LSMESTIMATE tmt 'A vs B: Overall'  1 -1 / cl;
RUN;
```

Notes:

- Change represents the change from baseline to each visit of the variable;
- Tmt represents the treatment group;
- Visit represents the clinic visit;
- Country represents the (pooled) Country;
- 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 normal at baseline
- Smoking represents the smoking status at Screening;
- Baseline represents the baseline value of the variable;
- Patient represents the Patient Number;
- Treatment order: 1 = CHF 5993 pMDI, 2 = Budesonide/formoterol.

Tables that require ANCOVA model for changes from pre-dose to post-dose for spirometry and 95% CIs of differences between treatments:

```
PROC MIXED data = dataset;
    By VISIT;
    CLASS tmt country n_COPD_exac airflow_sev smoking;
    MODEL change = tmt country n_COPD_exac airflow_sev smoking predose;
    LSMEANS tmt / om cl at means;
    LSMESTIMATE tmt 'A vs B' 1 -1 / cl;
RUN;
```

Notes:

- Change represents the change from pre-dose to post-dose at each visit of the variable;
- Tmt represents the treatment group;
- Visit represents the clinic visit;
- Country represents the (pooled) Country;
- 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 normal at baseline
- Smoking represents the smoking status at Screening;
- Predose represents the pre-dose value of the variable at each visit;
- Treatment order: 1 = CHF 5993 pMDI, 2 = Budesonide/formoterol.

Tables that require linear mixed model for repeated measures for diary data – rescue medication and 95% CIs of differences between treatments:

```
PROC MIXED data = dataset;
    CLASS tmt visit country n_COPD_exac airflow_sev smoking patient;
    MODEL change = tmt visit tmt*visit country 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,
        'A vs B: Week 24'  0 0 0 1 0 0 0 -1,
        'A: Overall' 4 8 6 6 0 0 0 0 divisor=24,
        'B: Overall' 0 0 0 0 4 8 6 6 divisor=24,
        'A vs B: Overall'   4 8 6 6 -4 -8 -6 -6 divisor=24 / om at means cl;
RUN;
```

Notes:

- Change represents the change from baseline to each inter-visit period of the variable;
- Tmt represents the treatment group;

- Visit represents the inter-visit period;
- Country represents the (pooled) Country;
- 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 normal at baseline
- Smoking represents the smoking status at Screening;
- Baseline represents the baseline value of the variable;
- Patient represents the Patient Number;
- Treatment order: 1 = CHF 5993 pMDI, 2 = Budesonide/formoterol.

5 TABLES AND LISTINGS

The raw statistical output from SAS for the analyses will be provided as an appendix for internal use only and not for inclusion into the CSR.

5.1 Output Format

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page separated by a horizontal line.

The *sponsor name*, *protocol number,* programmers User ID, status of the table/listing (i.e., draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left. The dataset used in listings will be displayed including the time stamp of dataset creation. If more than one dataset used for a particular listing, the list of dataset will be separated by a comma (“,”).

The first line in the document header will display the *sponsor name*, *protocol number* followed by the *figure number* and the *title* of the figure. The source table number will appear in the footer following by figure specific footnotes. For all the figures, with the only exception of forest plots, the following specifications should be applied:

- height = 17.5 cm;
- width = 19 cm;
- font size = 10-point.

Further, figures will be produced as high resolution graphs using the IMAGE_DPI option in SAS, by setting it =600.

A *landscape layout* is proposed for all presentations (except for figures) and will be produced in rich text format (RTF) (i.e., they will tabular in format).

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9cm from the right. The *top and bottom margins* will be a minimum 2.92cm.

A *9-point* font size for tables and *7* or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size=141 and page size=44 for *8-point* font size, and line size=161 and page size=50 for *7-point* will be used so as to fit on both UK and US paper sizes.

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.

Tables, listings, and figures document name will follow the format of:

- Triversyti_DryRun_1_<Tables, Listings, Figures>_YYYYMMDD.doc
- …
- Triversyti_DryRun_4_<Tables, Listings, Figures>_YYYYMMDD.doc
- Triversyti_FinalAnalysis_<Tables, Listings, Figures>_YYYYMMDD.doc

- Triversyti_FinalAnalysis_<Tables, Listings, Figures>_YYYYMMDD.doc
- Triversyti_FinalAnalysis_<Tables, Listings, Figures>_YYYYMMDD.doc

5.2 Quality Control of Outputs

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PPD procedures which includes the following steps to ensure the quality of the outputs:

- The author of each table/listing/figure program will review the programs and will verify that no error message is highlighted in the 'LOG' file.
- Tables, figures and listings will be independently programmed by a second programmer / statistician and outputs will be compared electronically (by comparing the data being tabulated using PPD validated programs).
- All outputs will be compared to the shells.
- Related outputs will be compared for consistency.

5.3 Conventions

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):

- BMI, duration of smoking (years), duration of the treatment of COPD exacerbations with systemic steroids and antibiotics, and of hospitalisation for COPD exacerbations (days), exposure (days): whole numbers;
- time to discontinuation (weeks), time since first COPD diagnosis (years), time since last documented COPD exacerbation (months), SGRQ scores, compliance, time to first COPD exacerbation (weeks), average use of rescue medication (daily mean number of puffs), percentage of days without intake of rescue medication, average HR (bpm), average QTcF (ms), average PR (ms), average QRS (ms): 1 decimal place;
- reversibility in FEV_1 (L), EQ-5D-3L index: 2 decimal places;
- change from baseline/screening/pre-dose: 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), adjusted difference between means and its confidence limits, SD, median, first and third quartiles: actual data + 1 decimal place (with the exception of health economic data: actual data + 2 decimal places).

Note: for average HR, QTcF, PR and QRS obtained for each patient from the triplicate 12-lead ECG at Visit 2 pre-dose, the number of decimal places of actual data will be assumed = 1;

- 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;
- pneumonia rate: 3 decimal places;
- total follow-up time in the tables on pneumonias: 2 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), adjusted rate ratio and its confidence limits: 3 decimal places.

In general, the maximum number of decimal places reported shall be four for any summary statistic.

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

P-values, if applicable, will be presented to 3 decimal places. If a p-value is less than 0.05 but is greater than or equal to 0.01, then an asterisk (*) will be added next to this value. If a p-value is less than 0.01 but is greater than or equal to 0.001, then two asterisks (**) will be added next to this value. Finally, if the p-value is less than 0.001 then three asterisks (***) will be added next to this value and it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999.

In all the listings, a column with a flag (@) for treatment misallocation will identify the treatment misallocations.

Unless otherwise stated, listings will be presented by patient ID (9-digit) followed by the randomised treatment. Patient ID and Country will be presented on all listings.

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.

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.

All tables will have their source listing referenced in a footnote. Listings should be sorted by patient and visit (unless otherwise specified) and have the SDTM and/or ADaM source data referenced in

a footnote. All tables, listings and figures will be converted into Microsoft Word documents and collated into three complete documents. If the listings are too large to be included in one file they will be separated into manageable sized files.

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

6 REFERENCES

[1] Huchon G1, Magnussen H, Chuchalin A, Dymek L, Gonod FB, Bousquet J. Lung function and asthma control with beclometasone and formoterol in a single inhaler.Respir Med. 2009 Jan;103(1):41-9.

[2] Calverley PM, Kuna P, Monsó E, Costantini M, Petruzzelli S, Sergio F, Varoli G, Papi A, Brusasco V. Beclometasone/formoterol in the management of COPD: a randomised controlled trial.Respir Med. 2010 Dec;104(12):1858-68

[3] Dolan P. Modeling valuations for EuroQol health states. Med Care 1997; 35(11):1095-1108.

[4] Pocock S. (1977). Group sequential methods in the design and analysis of clinical trials. Biometrika, 64: 191-9.

[5] Gernot Wassmer, Werner Brannath. Group Sequential and Confirmatory Adaptive Designs in Clinical Trials. Springer 2016.

[6] Christopher Jennison, Bruce W. Turnbull. Group sequential methods with applications to clinical trials. Chapman & Hall / CRC 2000.

APPENDIX I: ST. GEORGE'S RESPIRATORY QUESTIONNAIRE

Please tick in one box to show how you describe your current health (not used in total or domain score calculations):

Response	
Very good	☐
Good	☐
Fair	☐
Poor	☐
Very poor	☐

ITEM WEIGHTS

PART 1

1) Over the past 4 weeks, I have coughed:

Response	**Weight**
Most days a week	80.6
Several days a week	63.2
A few days a month	29.3
Only with chest infections	28.1
Not at all	0.0

2) Over the past 4 weeks, I have brought up phlegm (sputum):

Response	**Weight**
Most days a week	76.8
Several days a week	60.0
A few days a month	34.0
Only with chest infections	30.2
Not at all	0.0

3) Over the past 4 weeks, I have had shortness of breath:

Response	**Weight**
Most days a week	87.2
Several days a week	71.4
A few days a month	43.7
Only with chest infections	35.7
Not at all	0.0

4) Over the past 4 weeks, I have had attacks of wheezing:

Response	Weight
Most days a week	86.2
Several days a week	71.0
A few days a month	45.6
Only with chest infections	36.4
Not at all	0.0

5) During the past 4 weeks, how many severe or very unpleasant attacks of chest trouble have you had?

Response	Weight
More than three attacks	86.7
3 attacks	73.5
2 attacks	60.3
1 attack	44.2
No attacks	0.0

6) How long did the worst attack of chest trouble last?

Response	Weight
A week or more	89.7
3 or more days	73.5
1 or 2 days	58.8
Less than a day	41.9

7) Over the past 4 weeks, in an average week, how many good days (with little chest trouble) have you had?

Response	Weight
No good days	93.3
1 or 2 good days	76.6
3 or 4 good days	61.5
Nearly every day is good	15.4
Every day is good	0.0

8) If you have a wheeze, is it worse in the morning?

Response	Weight
No	0.0
Yes	62.0

PART 2

Section 1

How would you describe your chest condition?

Response	Weight
The most important problem I have	83.2
Causes me quite a lot of problems	82.5
Causes me a few problems	34.6
Causes no problem	0.0

If you have ever had paid employment.

Response	Weight
My chest trouble made me stop work altogether	88.9
My chest trouble interferes with my work or made me change my work	77.6
My chest trouble does not affect my work	0.0

Section 2

Questions about what activities usually make you feel breathless these days.

Response	Weight
Sitting or lying still	90.6
Getting washed or dressed	82.8
Walking around the home	80.2
Walking outside on the level	81.4
Walking up a flight of stairs	76.1
Walking up hills	75.1
Playing sports or games	72.1

Section 3

Some more questions about your cough and breathlessness these days.

Response	Weight
My cough hurts	81.1
My cough makes me tired	79.1
I am breathless when I talk	84.5
I am breathless when I bend over	76.8
My cough or breathing disturbs my sleep	87.9
I get exhausted easily	84.0

Section 4

Questions about other effects that your chest trouble may have on you these days.

Response	Weight
My cough or breathing is embarrassing in public	74.1
My chest trouble is a nuisance to my family, friends or neighbours	79.1
I get afraid or panic when I cannot get my breath	87.7
I feel that I am not in control of my chest problem	90.1
I do not expect my chest to get any better	82.3
I have become frail or an invalid because of my chest	89.9
Exercise is not safe for me	75.7
Everything seems too much of an effort	84.5

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

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

Section 6

These are questions about how your activities might be affected by your breathing.

Response	Weight
I take a long time to get washed or dressed	74.2
I cannot take a bath or shower, or I take a long time	81.0
I walk slower than other people, or I stop for rests	71.7
Jobs such as housework take a long time, or I have to stop for rests	70.6
If I walk up one flight of stairs, I have to go slowly or stop	71.6
If I hurry or walk fast, I have to stop or slow down	72.3
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	74.5
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	71.4
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	63.5

Section 7

We would like to know how your chest usually affects your daily life.

Response	Weight
I cannot play sports or games	64.8
I cannot go out for entertainment or recreation	79.8
I cannot go out of the house to do the shopping	81.0
I cannot do housework	79.1
I cannot move far from my bed or chair	94.0

Please write in any other important activities that your chest trouble may stop you doing (not used in total or domain score calculations):

Now would you tick in the box (one only) which you think best describes how your chest affects you:

Response	Weight
It does not stop me doing anything I would like to do	0.0
It stops me doing one or two things I would like to do	42.0
It stops me doing most of the things I would like to do	84.2
It stops me doing everything I would like to do	96.7

Scoring Algorithm

Three domain scores are calculated: **Symptoms, Activity, Impacts.**

One **Total** score is also calculated.

PRINCIPLE OF CALCULATION

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

Each domain of the questionnaire is scored separately in three steps:

i. The weights for all items with positive responses are summed.

ii The weights for missed items are deducted from the maximum possible weight for each domain. The weights for all missed items are deducted from the maximum possible weight for the Total score.

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

$$\text{Score} = \frac{\text{Summed weights from positive items in that domain}}{\text{Sum of weights for all items in that domain}} * 100$$

The Total score is calculated in similar way:

$$\text{Score} = \frac{\text{Summed weights from positive items in the questionnaire}}{\text{Sum of weights for all items in the questionnaire}} * 100$$

Sum of maximum possible weights for each domain and Total:

Symptoms	662.5
Activity	1209.1
Impacts	2117.8
Total	3989.4

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

SYMPTOMS DOMAIN

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

ACTIVITY DOMAIN

This is calculated from the summed weights for the positive responses to sections 2 and 6 of Part 2.

IMPACTS DOMAIN

This is calculated from the summed weights for the positive responses to sections 1, 3, 4, 5, 7 of Part 2.

TOTAL SCORE

The Total score is calculated by summing all positive responses in the questionnaire.

HANDLING MISSING ITEMS

The following methods will be used:

Symptoms

The Symptoms domain will tolerate a maximum of 2 missed items. 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

The Activity domain will tolerate a maximum of 4 missed items. 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

The Impacts domain will tolerate a maximum of 6 missed items. 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).

APPENDIX II: COMMON NAME AND THE ASSOCIATED PREFERRED NAMES

Common name	Preferred Names
"SALBUTAMOL"	"SALBUTAMOL" "SALBUTAMOL SULFATE"
"FENOTEROL"	"FENOTEROL" "FENOTEROL HYDROBROMIDE"
"SALMETEROL"	"SALMETEROL" "SALMETEROL XINAFOATE"
"FORMOTEROL"	"FORMOTEROL" "FORMOTEROL FUMARATE"
"INDACATEROL"	"INDACATEROL" "INDACATEROL MALEATE"
"FLUTICASONE W/SALMETEROL"	"FLUTICASONE W/SALMETEROL (FLUTICASONE,SALMETEROL)" "SERETIDE (FLUTICASONE PROPIONATE,SALMETEROL XINAFOATE)"
"BUDESONIDE W/FORMOTEROL"	"BUDESONIDE W/FORMOTEROL (BUDESONIDE,FORMOTEROL)" "BUDESONIDE W/FORMOTEROL FUMARATE (BUDESONIDE,FORMOTEROL FUMARATE)"
"BECLOMETASONE W/FORMOTEROL"	"BECLOMETASONE DIPROPIONATE/FORMOTEROL FUMARATE" "BEKFORM (BECLOMETASONE DIPROPIONATE,FORMOTEROL FUMARATE)"
"FLUTICASONE W/VILANTEROL"	"BREO ELLIPTA (FLUTICASONE FUROATE,VILANTEROL TRIFENATATE)"
"FLUTICASONE W/FORMOTEROL"	"FORMOSONE (FLUTICASONE PROPIONATE,FORMOTEROL FUMARATE)"
"MOMETASONE W/FORMOTEROL"	"FORMOTEROL W/MOMETASONE (FORMOTEROL,MOMETASONE)" "DULERA (FORMOTEROL FUMARATE,MOMETASONE FUROATE)"
"FENOTEROL W/IPRATROPIUM"	"DUOVENT (FENOTEROL HYDROBROMIDE,IPRATROPIUM BROMIDE)" "FENOTEROL W/IPRATROPIUM (FENOTEROL,IPRATROPIUM)" "FENOTEROL W/IPRATROPIUM BROMIDE (FENOTEROL,IPRATROPIUM BROMIDE)"
"IPRATROPIUM W/SALBUTAMOL"	"COMBIVENT (IPRATROPIUM BROMIDE,SALBUTAMOL SULFATE)" "NEBU IPRASAL (IPRATROPIUM BROMIDE MONOHYDRATE,SALBUTAMOL SULFATE)"
"GLYCOPYRRONIUM W/INDACATEROL"	"ULTIBRO (GLYCOPYRRONIUM BROMIDE,INDACATEROL MALEATE)"
"BECLOMETASONE"	"BECLOMETASONE" "BECLOMETASONE DIPROPIONATE"
"FLUTICASONE"	"FLUTICASONE" "FLUTICASONE PROPIONATE"
"IPRATROPIUM"	"IPRATROPIUM" "IPRATROPIUM BROMIDE" "IPRATROPIUM BROMIDE MONOHYDRATE"
"TIOTROPIUM"	"TIOTROPIUM" "TIOTROPIUM BROMIDE"
"MONTELUKAST"	"MONTELUKAST" "MONTELUKAST SODIUM"

APPENDIX III: RESULTS OF EFFICACY BORDER CALCULATION FOR INTERIM ANALYSIS

09:11 Friday, June 05, 2020 **89**

The SAS System

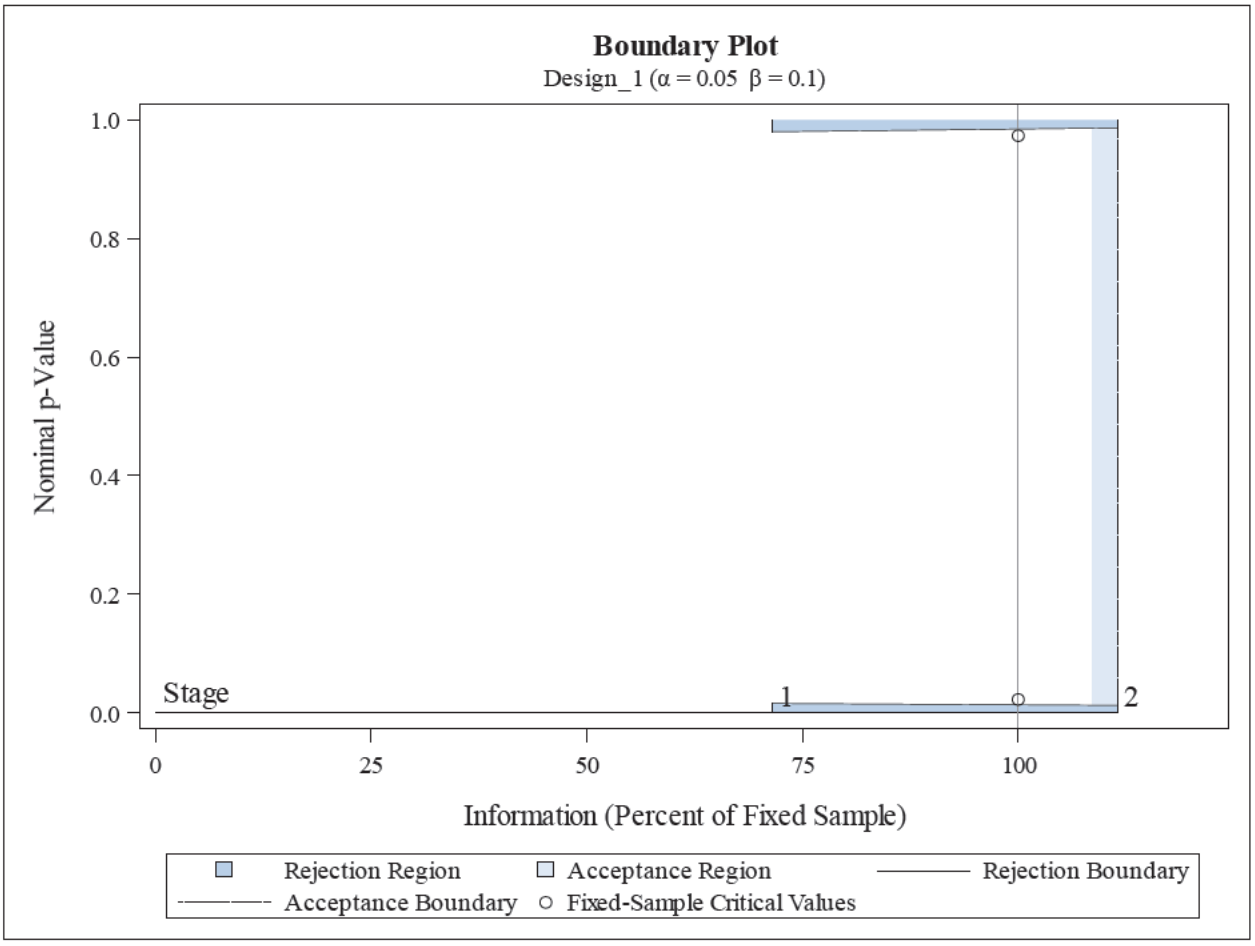
The SEQDESIGN Procedure
Design: Design_1

Design Information	
Statistic Distribution	Normal
Boundary Scale	p-Value
Alternative Hypothesis	Two-Sided
Early Stop	Reject Null
Method	Error Spending
Boundary Key	Both
Number of Stages	2
Alpha	0.05
Beta	0.1
Power	0.9
Max Information (Percent of Fixed Sample)	111.4018
Null Ref ASN (Percent of Fixed Sample)	109.9193
Alt Ref ASN (Percent of Fixed Sample)	81.70757

Method Information

Boundary	Method	Alpha	Beta	Error Spending Function	Drift
Upper Alpha	Error Spending	0.02500	0.10000	Approx Pocock	3.421312
Lower Alpha	Error Spending	0.02500	0.10000	Approx Pocock	-3.42131

Boundary Information (p-Value Scale) Null Reference = 0					
	Information Level	Alternative		Boundary Values	
		Reference		Lower	Upper
Stage	Proportion	Lower	Upper	Alpha	Alpha
1	0.6420	-2.74132	2.74132	0.01859	0.98141
2	1.0000	-3.42131	3.42131	0.01252	0.98748



Error Spending Information

	Information Level	Cumulative Error Spending			
		Lower		Upper	
Stage	Proportion	Alpha	Beta	Beta	Alpha
1	0.6420	0.01859	0.00000	0.00000	0.01859
2	1.0000	0.02500	0.10000	0.10000	0.02500