NCT02676089

Statistical Analysis Plan

Chiesi Farmaceutici S.p.A.

Protocol: CCD-05993AB2-02

EudraCT: 2015-000717-40

Treatment: CHF 5993 pMDI 200/6/12.5 µg

A 52 WEEK, RANDOMIZED, DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, ACTIVE CONTROLLED, 3-ARM PARALLEL GROUP TRIAL COMPARING CHF 5993 200/6/12.5 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE PLUS GLYCOPYRRONIUM BROMIDE) TO CHF 1535 200/6 µg pMDI (FIXED COMBINATION OF EXTRAFINE BECLOMETHASONE DIPROPIONATE PLUS FORMOTEROL FUMARATE) ALONE OR ON TOP OF OPEN-LABEL TIOTROPIUM 2.5 µg RESPIMAT® IN PATIENTS WITH ASTHMA UNCONTROLLED ON HIGH DOSES OF INHALED CORTICOSTEROIDS IN COMBINATION WITH LONG-ACTING ß2-AGONISTS

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Abbreviations

AC	Adjudication Committee
ACQ	Asthma Control Questionnaire©
ADaM	Analysis Dataset Model
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AV	Atrial Ventricular
BID	*Bis in die* (twice a day)
BDP	Beclometasone Dipropionate
B17MP	Beclometasone-17-monopropionate
BMI	Body Mass Index
BPH	Benign Prostatic Hyperplasia
bpm	Beats Per Minute
BTPS	Body Temperature and Pressure, Saturated (conditions)
BUN	Blood Urea Nitrogen
Ca	Calcium
CI	Confidence Interval
Cl	Chloride
CS	Clinically Significant
CRO	Contract Research Organization
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EoT	End of Treatment
EQ-5D-3L	European Quality of Life-5 Dimensions-3 Levels
FEV_1	Forced Expiratory Volume in 1 Second
FF	Formoterol Fumarate
FPFV	First Patient First Visit
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GB	Glycopyrronium Bromide
GINA	Global Initiative for Asthma
GFR	Glomerular Filtration Rate
GOLD	Global Initiative for Chronic Obstructive Lung Disease
γ-GT	Gamma-Glutamyl Transpeptidase
Hb	Haemoglobin
Hct	Haematocrit

HFA	Hydrofluoroalkane
HR	Heart Rate
IC	Inspiratory Capacity
ICS	Inhaled Corticosteroid
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISO	International Standards Organization
ITT	Intention-to-Treat
IUD	Intra Uterine Device
IUS	Intra Uterine System
K	Potassium
L	Liter
LABA	Long-Acting β2-Agonist
LAMA	Long Acting Muscarinic Antagonist
LMA	Leukotriene-Modifying Agent
LTRA	Leukotriene receptor antagonist
MACE	Major Adverse Cardiovascular Events
MAOI	Monoamine Oxidase Inhibitor
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
min	minute
ml	milliliter
ms	millisecond
MNAR	Missing not at Random
Na	Sodium
NCS	Not Clinically Significant
NYHA	New York Heart Association
P	Period
PEF	Peak Expiratory Flow
PLT	Platelet Count
pMDI	Pressurised Metered Dose Inhaler
PP	Per Protocol
PR	Time interval between the onset of the P wave and the beginning of the QRS complex
PV	Pharmacovigilance
PT	Preferred Term
QRS	Time interval between the beginning of the Q wave and the termination of the S wave
QTc	Time Interval Between the Q and T wave in the ECG (corrected for heart rate)
QTcF	Fridericia-corrected time interval between the Q and T waves
RBC	Red Blood Cell
RCT	Randomized Controlled Trial
RR	Time interval between two consecutive R waves
R&D	Research and Development
RTF	Rich Text Format
SAE	Serious Adverse Event

SAMA	Short-Acting Muscarinic Antagonist
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVC	Slow Vital Capacity
TEAE	Treatment Emergent Adverse Event
TLC	Total Lung Capacity
µg	microgram
V	Visit
VAS	Visual Analogue Scale
VC	Vital Capacity
WBC	White Blood Cell
WHO	World Health Organisation

1 Introduction

This document presents the statistical analysis plan (SAP) for Chiesi Farmaceutici S.p.A., Protocol No. CCD-05933AB2-02: a 52 week, randomized, double blind, multinational, multicentre, active controlled, 3-arm parallel group trial comparing CHF5993 200/6/12.5 µg pMDI (fixed combination of extrafine beclomethasone dipropionate plus formoterol fumarate plus glycopyrronium bromide) to CHF 1535 200/6 µg pMDI (fixed combination of extrafine beclomethasone dipropionate plus formoterol fumarate) alone or on top of open-label tiotropium 2.5 µg Respimat® in patients with asthma uncontrolled on high doses of inhaled corticosteroids in combination with long-acting ß2-agonists.

This analysis plan is based on the final protocol (version 2.0) dated 12 May 2016 and the final electronic case report form (eCRF) (version 6.0) dated 18 May 2017.

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

Note: information regarding the health economic analysis will be reported separately and does not form part of this SAP.

2 Study Objectives

The primary objectives of this study are:

- To demonstrate the superiority of CHF 5993 200/6/12.5 pMDI compared to CHF 1535 200/6 pMDI in terms of change from baseline in pre-dose FEV_1 at Week 26;
- To demonstrate the reduction of moderate and severe asthma exacerbation rate with CHF 5993 200/6/12.5 pMDI compared to CHF 1535 200/6 pMDI during the entire 52-week treatment period.

The key secondary objectives of this study are:

- To demonstrate the superiority of CHF 5993 200/6/12.5 pMDI compared to CHF 1535 200/6 pMDI in terms of change from baseline in peak FEV_1 within 3 hours post-dose at Week 26.
- To demonstrate the superiority of CHF 5993 200/6/12.5 compared to CHF 1535 200/6 in terms of change from baseline in morning PEF averaged over the 26-week treatment period.
- To demonstrate the reduction of severe asthma exacerbation rate with CHF 5993 200/6/12.5 pMDI compared to CHF 1535 200/6 pMDI during the entire 52-week treatment period in the pooled analysis of CCD-05993AB1-03 and CCD-05993AB2-02 trials.

The other secondary objectives of this study are:

- To compare CHF 5993 200/6/12.5 to CHF 1535 200/6 for other lung function assessments, patient's health status and clinical outcome measures.
- To compare CHF 5993 200/6/12.5 to CHF 1535 200/6 + Tiotropium for lung function assessments, patient's health status and clinical outcome measures.
- To collect data in order to assess the impact of study treatments on health economic outcomes.
- To assess the safety and the tolerability of the study treatments.

2.1 Primary Efficacy Variables

The primary efficacy variables of this study are:

- Change from baseline in pre-dose FEV_1 at Week 26
- Moderate and severe asthma exacerbation rate over 52-week treatment period

2.2 Key Secondary Efficacy Variables

The key secondary efficacy variables of this study are:

- Change from baseline in peak FEV_1 (within 3 hours post-dosing) at Week 26
- Change from baseline in the average morning PEF measured by patients at home over the 26-week treatment period (i.e., up to Week 26)

- Severe asthma exacerbation rate over 52-week treatment period in a pre-specified pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02

2.3 Other Secondary Efficacy Variables

The other secondary efficacy variables of this study are:

- Change from baseline in peak FEV_1 (within 3 hours post-dosing) at all clinical visits
- Change from baseline in pre-dose FEV_1 at all clinical visits
- FEV_1 response (change from baseline in pre-dose $FEV_1 \geq 100$ ml) at Week 26 and Week 52
- Change from baseline in FEV_1 $AUC_{0\text{-}3h}$ normalised by time at all clinical visits
- Change from baseline in the ACQ-7 score at all clinical visits
- ACQ-7 response (change from baseline in ACQ-7 score $\leq$ -0.5) at Week 26 and Week 52
- Change from baseline in morning and evening PEF in each inter-visit period, over the 26-week treatment period (evening PEF) and over the 52-week treatment period
- Time to first moderate or severe asthma exacerbation
- Time to first severe asthma exacerbation in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02
- Moderate asthma exacerbation rate over the 52-week treatment period in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02
- Time to first moderate asthma exacerbation in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02
- Moderate and severe asthma exacerbation rate over the 52-week treatment period in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02
- Time to first moderate or severe asthma exacerbation in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02
- Moderate asthma exacerbation rate over the 52-week treatment period
- Time to first moderate asthma exacerbation
- Change from baseline in the average use of rescue medication (number of puffs/day) in each inter-visit period, over the 26-week treatment period and over the 52-week treatment period
- Change from baseline in the percentage of rescue medication-free days in each inter-visit period, over the 26-week treatment period and over the 52-week treatment period
- Change from baseline in the average daily asthma symptoms scores in each inter-visit period, over the 26-week treatment period and over the 52-week treatment period

- Change from baseline in the percentage of asthma symptom free-days in each inter-visit period, over the 26-week treatment period and over the 52-week treatment period
- Change from baseline in the percentage of asthma control days in each inter-visit period, over the 26-week treatment period and over the 52-weeks treatment period

2.4 Exploratory Efficacy Variable

The exploratory efficacy variable of this study is:

- Pre-dose FVC, IC and VC at all clinical visits.

2.5 Health Economic Variables

The health economic variables of this study are:

- European Quality of Life-5 Dimensions-3 Levels (EQ-5D-3L) visual analogue scale (VAS) score and EQ-5D-3L index at all clinical visits;
- Number of hospital admissions due to asthma;
- Number of hospital days due to asthma;
- Number of emergency room visits due to asthma;
- Number of unscheduled contacts with health care providers due to asthma:
  - Family practitioner
  - Specialist outpatient setting
  - Specialist hospital outpatient setting
- Unplanned diagnostic tests or instrumental tests due to asthma
- Concomitant medications
- Lost productivity (sick leave days from work, retirement) due to asthma

Note: information regarding additional analyses on health economic data will be reported separately and does not form part of this SAP.

2.6 Safety Variables

The safety variables of this study are:

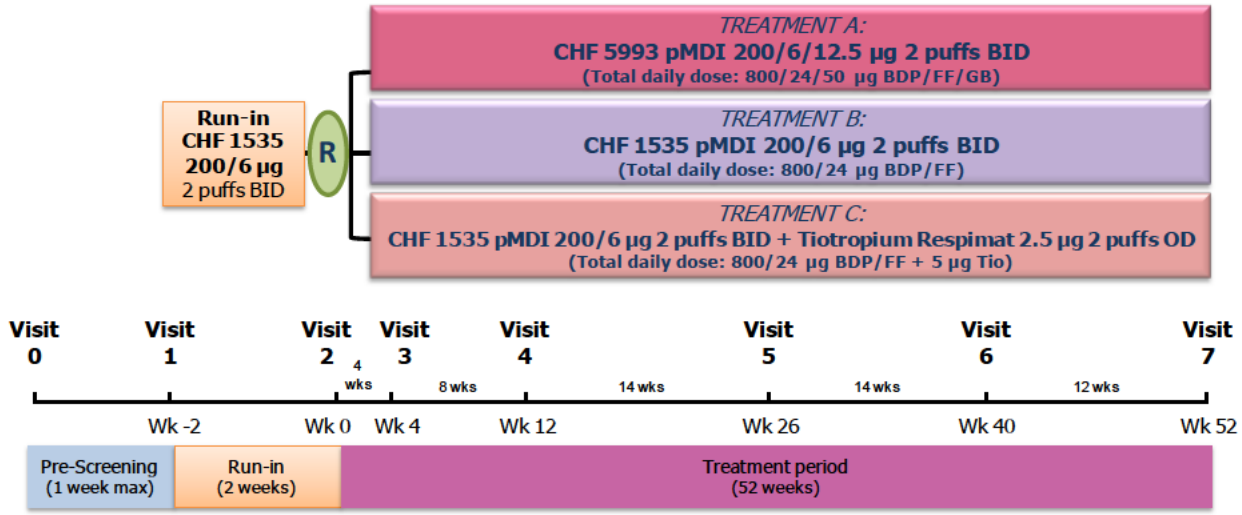
- Adverse events (AEs) and adverse drug reactions (ADRs).
- Vital signs (systolic and diastolic blood pressure).
- 12-lead ECG parameters: heart rate (HR), QTcF, PR and QRS.
- Average 24-hour Heart Rate derived from ECG Holter (on a subset of at least 10% of the randomised patients).
- Standard haematology and blood chemistry.

3 Study Design

3.1 Discussion of Study Design

This is a phase III, multicentre, randomised, double-blind, with an open label arm, active-controlled, 3-arm parallel group study in asthmatic patients. Approximately 1435 randomised patients in about 250 sites will be involved.

The study duration for each patient will be up to 55 weeks as depicted below:



Note: only the group C is an open-label arm (with CHF 1535 pMDI and Tiotropium Respimat®).

During the visits of the randomised treatment period (V2 to V7), patients will undergo serial spirometry assessments under supervision (over 3-hour post-dose):

- Time "0" (T-0) is defined as the time of first inhalation of study medication.
- The 7 time points are: -45min; -15min; 15min; 30min; 60min; 120min and 180min.

3.2 Study Treatments

3.2.1 Run-in Period

- CHF 1535 pMDI 200/6 µg: 2 inhalations BID (Total daily dose: BDP 800µg/FF 24µg)

3.2.2 Randomised Treatment Period

- CHF 5993 pMDI 200/6/12.5 µg: 2 inhalations BID (Total daily dose: BDP 800µg/FF 24µg/GB 50µg)
- CHF 1535 pMDI 200/6 µg: 2 inhalations BID (Total daily dose: BDP 800µg/FF 24µg)
- CHF 1535 pMDI 200/6 µg + tiotropium Respimat® (Spiriva® Respimat®):
  - 2 inhalations BID CHF 1535 pMDI (Total daily dose: BDP 800µg/FF 24µg)
  - 2 inhalations OD tiotropium (Total daily dose: tiotropium 5 µg)

3.2.3 Rescue Medication

Salbutamol (100 µg/puff) will be used as rescue medication only in case of absolute need.

3.3 Study Schedule

A total of 8 clinic visits (Visit 0 to Visit 7) will take place during the study:

- A **pre-screening visit (Visit 0)** to explain the aim of the study to the patients, to obtain their written informed consent and to prepare patients for V1;
- A **screening visit (Visit 1)**, no more than 7 days after V0 (Week -2 before randomisation), to verify the patients' eligibility. This visit will be followed by a 2-week run-in period, where the patients will receive open-label CHF 1535 200/6 µg;
- A **randomisation visit (Visit 2, Week 0)** when patients will be randomised to one of the three treatment arms (CHF 5993 200/6/12.5 µg or CHF 1535 200/6 µg or CHF 1535 200/6 µg + tiotropium 2.5µg).
- Five **subsequent visits** scheduled during the treatment period after 4 (**Visit 3**), 12 (**Visit 4**), 26 (**Visit 5**), 40 (**Visit 6**) and 52 (**Visit 7**) weeks of treatment.

The visits shall be performed with appropriate wash-out of medications. In case the wash-out of medications is not respected:

- at Visit 1 and Visit 2, the visit can be rescheduled once within 2 days. If, in the morning of the rescheduled visit, the wash-out is still not respected the patient will be discontinued;
- at Visit 3 to Visit 7, the visit will be rescheduled within 3 days in order to obtain proper medication wash-out.

Note:

- Unscheduled visits/tests can be performed during the study at the discretion of the Investigator. The relevant information will be collected in the eCRF.
- In case the reversibility test is negative at Visit 1, it should be performed again during run-in period (once before randomisation), after an appropriate wash-out from bronchodilators (6 hours) and run-in medication (12 hours). The relevant information will be collected in the eCRF.

In addition:

- A subset of patients (at least 10 % of randomised patients) will have a 24-hour ECG holter at **V1** (**screening**), **V2** (**randomisation**), **V4** (**Week 12**), **V5** (**Week 26**) and **V7** (**Week 52**).

The study plan and scheduled tests are summarised in the following flow-chart:

	Pre-screening	Run-in	Treatment Period					
Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7/ET***
Time (Wks)	**-3**	**-2**	**0**	**4**	**12**	**26**	**40**	**52**
Windows (Days)			**±2d**	**±3d**	**±5d**	**±10d**	**±5d**	**±5d**
Assessments								
Informed consent procedures	**X**							
Instructions for the screening visit	**X**							
Demographic data collection	**X**							
Inclusion/Exclusion criteria		**X**	**X**					
Medical history/Previous medications		**X**						
Concomitant medications		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Events/Serious adverse events		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Physical examination		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Weight & Height		**X**						
Vital signs (BP) pre-dose/post-dose [1]		**X**	**X**	**X**	**X**	**X**	**X**	**X**
12-lead ECG (single) pre-dose/post-dose [2]		**X**	**X**	**X**	**X**	**X**	**X**	**X**
24h holter (subset of patients) [3]		**X**	**X**		**X**	**X**		**X**
Pre-dose spirometry [4]		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Reversibility testing [5]		**X**						
Post-dose serial spirometry (0-3 hours) [6]			**X**	**X**	**X**	**X**	**X**	**X**
ACQ-7		**X**	**X**	**X**	**X**	**X**	**X**	**X**
EQ-5D-3L questionnaire			**X**	**X**	**X**	**X**	**X**	**X**
Health Economics			**X**	**X**	**X**	**X**	**X**	**X**
Haematology and blood chemistry		**X**				**X**		**X**
Serum pregnancy test		**X**						**X**
Urinary pregnancy test		**X**	**X**	**X**	**X**	**X**	**X**	
Home PEF (predose)		**X (daily am/pm)**						
Electronic diary completion (asthma symptoms, treatment compliance, rescue intake)		**X (daily am/pm)**						
Electronic diary review [7]			**X**	**X**	**X**	**X**	**X**	**X**
Assessment of asthma exacerbations		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Training to the use of pMDI/Respimat [8]		**X**	**X**					
Training to the use of Aerochamber Plus [8]		**X**	**X**					
Training on recognition of a developping asthma exacerbation [8]		**X**	**X**					
Training to the use of ediary/epeakflowmeter [8]		**X**	**X**					
IRT	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Run-in dispensation (D) /Collection (C)		**D**	**C**					
Study drug dispensation (D) /Collection (C)			**D**		**D/C**	**D/C**	**D/C**	**C**
Spacer dispensation (D) /Collection (C) [9]		**D**	**D/C**			**D/C**		**C**

* ET stands for Early Termination (pre-dose assessments will be performed/ post-dose assessments only if appropriate)

1. SBP and DBP after 10 min rest in sitting position. Pre-dose at V1. Pre and post-dose (45 min) from V2 to V7.
2. ECG in single. Pre-dose at V1. Pre and post-dose (45 min) from V2 to V7.
3. In a subset of at least 10 % of randomised patients.
4. FEV_1, FVC at 45 min and 15 min pre-dose (only V2 to V7). IC and VC to be done before FEV_1 & FVC (only V2 to V7).
5. Reversibility after 4x100 µg salbutamol.
6. FEV_1, FVC: serial spirometry at 15 min, 30 min, 60 min, 120 min and 180 min post-dose.
7. Regular check by the investigator and/or designee. Phone call(s) to the patient will be done in case of bad compliance and/or asthma control worsening.
8. Re-trainings can be done during the study if need be. Training for spacer only for patients who use it.
9. Spacer (Aerochamber) only dispensed for patients who use it.

The end of the trial is defined as the last visit (Visit 7) of the last patient in the trial.

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 randomised patients who receive at least one dose of the study treatment.

3.5.2 Intention-to-Treat (ITT) Population

The ITT population is defined as all randomised patients who receive at least one dose of the study treatment and with at least one available evaluation of efficacy (primary or secondary efficacy variables) after the baseline.

3.5.3 Per Protocol (PP) Population

The PP population is defined as all patients from the ITT population without any major protocol deviation (e.g., wrong inclusions, poor compliance, non-permitted medications).

Exact definition of major protocol deviations will be discussed by the study team during the blind review of the data and described in the Data Review Report.

3.5.4 Other Populations Defined for Tables and Listings

For the purposes of tables and listings a further four populations are defined:

- All screened patients;
- Screening failure patients;
- Randomised population (all randomised patients);
- Holter subset (all patients included in the Safety population selected for the 24 h Holter monitoring).

3.6 Withdrawn Patients

If a patient is withdrawn/drops-out of the study after receiving the test treatment, the patient study number and corresponding test treatments 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 to one of the three treatment arms with a 2:2:1 ratio. An Interactive Response Technology (IRT) system will be used at each visit (from pre-screening to follow-up call) to record patient status.

Patient number will be centrally assigned, through the IRT, during the pre-screening visit (Visit 0). Patient numbers will consist of a 9 digit-number:

- the 6 first digits correspond to the centre number (first 3 digits for the country number corresponding to the ISO country codes and 3 last progressive for the site - starting with an 8);
- the 3 last digits to the screening number (allocated in a chronological way in each site).

The Investigator, or designee, at the sites will call the IRT system to screen, randomise patients and assign treatment kits according to the sequence described in the randomisation list. The IRT will track also patient screen failures and discontinuations from the study.

3.8 Blinding

The randomization list will be provided to the labelling facility but 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, unless in case of emergency. The Sponsor's clinical team will also be blinded during the study as they will not have direct access to the randomization list.

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

3.9 Sample Size

The sample size has been calculated to demonstrate:

- the superiority of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 pMDI in terms of both co-primary endpoints
- the superiority of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 pMDI in terms of the key secondary endpoints

A total of 1435 patients will be randomised according to a 2:2:1 ratio to CHF 5993 200/6/12.5 pMDI (574 patients), CHF 1535 200/6 pMDI (574 patients) or CHF 1535 200/6 pMDI plus Tiotropium (287 patients).

A log-normal distribution is assumed for drop-out time, estimating approximately 13% drop-out rate at week 12, 16.5% at week 26 and 20% at week 52.

Approximately 1198 completed patients (479 per group in each of the CHF 5993 200/6/12.5 pMDI and CHF 1535 200/6 pMDI arms, and 240 in the CHF 1535 200/6 pMDI plus Tiotropium arm) will be available for the analysis at Week 26.

This sample size will provide:

- approximately 99% power to detect a mean difference of 90 ml in favour of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 pMDI in change from baseline in pre-dose FEV_1 at Week 26 at a two-sided significance level of 0.05, assuming a standard deviation (SD) of 311 ml;
- approximately 93% power to detect at Week 52 a rate ratio of 0.80 between CHF 5993 200/6/12.5 pMDI and CHF 1535 200/6 pMDI at a two-sided significance level

of 0.05 using a negative binomial model and assuming a rate of 2.70 moderate and severe asthma exacerbations per patient per year in the CHF 1535 200/6 group and an overdispersion parameter of the negative binomial distribution of 0.56.

The same number of patients will provide:

- approximately 99% power to detect a mean difference of 100 ml in favour of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 pMDI in peak FEV_1 change from baseline at Week 26 at a two-sided significance level of 0.05, assuming a SD of 338 ml.
- at least 99% power to detect a mean difference of 20 L/min in favour of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 pMDI in morning PEF change from baseline over the 26-week treatment period at a two-sided significance level of 0.05, assuming a SD of 45 L/min.
- approximately 86% power to detect at Week 52 a rate ratio of 0.80 between CHF 5993 200/6/12.5 pMDI and CHF 1535 200/6 pMDI at a two-sided significance level of 0.05, in the pooled analysis, using a negative binomial model and assuming a rate of 0.60 severe asthma exacerbations per patient per year in the CHF 1535 200/6 pMDI group and an overdispersion parameter of the negative binomial distribution of 0.56.

Since each patient with a follow-up of non-null duration provides a contribution to the analysis of asthma exacerbation rates, all randomized patients are considered to be evaluable, irrespective of whether they withdraw from the study prematurely.

Notes:

A total of at least 144 patients will be selected for the Holter recording.

4 Statistical Methodology

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:

- demographic characteristics will also be summarised on all randomised patients;
- ACQ-7 and efficacy variables derived from diary data will be summarised in the ITT population only;
- the medical history and the concomitant diseases will be summarised in the Safety and ITT populations only;
- the safety variables will be summarised in the Safety population only.

Since the superiority of CHF 5993 200/6/12.5 pMDI over CHF 1535 200/6 pMDI will be tested, the co-primary and the key secondary efficacy analyses will be based on the ITT population. These analyses will be also performed on the PP population for sensitivity purposes.

All 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.

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 rule will be applied: if a patient was randomised but received the incorrect treatment:

- the patient will be reported under the randomised treatment group for all analyses performed on the randomised 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 (i.e. an as-treated analysis will be performed). In case of treatment misallocation affecting only a specific period of the study, the patient will be reported under the treatment actually received for >50% of the duration of the randomised treatment period of the patient.

All the cases of treatment misallocation will be discussed during the Data Review Meeting and the decisions on the inclusion of study populations will be documented in the Data Review Report. All the cases of treatment misallocation will be reported in a specific listing.

4.1.2 Treatment Groups

Statistics will be displayed for the following treatment groups:

- CHF 5993 pMDI HS;
- CHF 1535 pMDI HS;
- CHF 1535 pMDI HS + Tiotropium;
- Overall (not applicable for compliance, concomitant and post-study medications, efficacy and safety analyses).

In the pooled analyses of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02, the following treatment groups will be considered:

- CHF 5993 pMDI + CHF 5993 pMDI HS;
    - CHF 5993 pMDI 100/6/12.5 µg ("CHF 5993 pMDI") data from study CCD-05993AB1-03 and CHF 5993 200/6/12.5 µg ("CHF 5993 pMDI HS") data from study CCD-05993AB2-02;
- CHF 1535 pMDI + CHF 1535 pMDI HS;
    - CHF 1535 pMDI 100/6 µg ("CHF 1535 pMDI") data from study CCD-05993AB1-03 and CHF 1535 200/6 µg ("CHF 1535 pMDI HS") data from study CCD-05993AB2-02.

4.1.3 Descriptive Statistics

Descriptive statistics for quantitative variables will include n (the number of non-missing values), mean, SD, median, minimum and maximum values. 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 at the alpha = 0.05 level (two-sided). Statistical significance will be declared if the p-value is less than 0.05.

4.1.5 Stratified Analyses

The analysis of co-primary efficacy variables (cf. section 4.7.1) and key secondary efficacy variables (cf. section 4.7.2) will be also performed for exploratory purpose on the ITT population stratifying by:

- Age group (< 65 years, ≥ 65 years);
- Gender (male or female);
- BMI (kg/m^2) at screening visit (< 25, [25-30), ≥ 30);

- Smoking status at screening (Non-smoker, Ex-smoker);
- Number of asthma exacerbations in the previous year (1, >1);
- Degree of reversibility at screening (delta FEV_1 : (200-400], > 400 ml);

AEs and Major Adverse Cardiovascular Events (MACEs) could be also analysed on the Safety population stratifying by:

- Age group (< 65 years, ≥ 65 years);
- BMI (kg/m^2) at screening visit (< 25, [25-30), ≥ 30);
- Use of spacer (Yes/No: spacer use during study as defined in section 4.4.3 will be considered);
- Relevant concomitant cardiovascular diseases (Presence only)

The following variables will be also summarised descriptively on the Safety population stratifying by use of spacer during study: 12-lead ECG HR and QTcF parameters, 24-hour Holter ECG average/minimum/maximum HR, longest and fastest tachycardia duration, longest and fastest tachycardia maximum HR, longest and slowest bradycardia duration, longest and slowest bradycardia minimum HR, slowest bradycardia duration and slowest bradycardia minimum HR variables will be also analysed on the Safety population stratifying by use of spacer prior to trial (Yes/No). Demographic characteristics will be also presented stratifying by inclusion in the Holter subset using the Safety population.

The following rule is currently proposed for selecting the relevant concomitant cardiovascular diseases: all the concomitant diseases in the 'Cardiac disorders' and 'Vascular disorders' system organ classes (SOCs), condition where AESOC/MHSOC in ("Cardiac disorders","Vascular disorders").

4.1.6 Definition of Baseline

The baseline value for the relevant variables is defined in the below table:

Table 1: Baseline calculations

Variable	Baseline
Pre-dose FEV_1	Baseline for pre-dose FEV_1 will be calculated as average of the FEV_1 measurements (L) from the V2Pre45min & V2Pre15min. If one of the two pre-dose values is missing, the baseline will be equal to the available pre-dose value.
Peak FEV_1	See pre-dose FEV_1.
Morning PEF	The derived morning "Best PEF" for the statistical analysis will be calculated for each morning session as the highest morning PEF value from all PEF measurements recorded pre-dose (see section 4.1.12) and with quality = "GOOD". The derived morning "Best PEF" for the statistical analysis will be calculated only for morning sessions recorded pre-dose and with at least two PEF measurements with quality = "GOOD". Baseline for morning PEF will be calculated as the average of all derived morning "Best PEF" values from the morning session of

	the day after Visit 1 to the morning session of the day of Visit 2 (inclusive). Standard rounding to the nearest integer will be applied. The baseline will be calculated if at least 7 derived morning "Best PEF" values will be available during the run-in period. The derived morning "Best PEF" value will be considered in the calculation.
FEV_1 response	The baseline used for the FEV_1 response calculation and as covariate in the statistical model is the baseline of pre-dose FEV_1.
FEV_1 AUC_{0-3h} normalised by time	See pre-dose FEV_1.
ACQ-7 score	Baseline will be the ACQ total score recorded at Visit 2.
ACQ-7 response	The baseline used for the ACQ-7 response calculation and as covariate in the statistical model is the baseline of ACQ-7 score.
Evening PEF	The derived evening "Best PEF" for the statistical analysis will be calculated for each evening session as the highest evening PEF value from all PEF measurements recorded pre-dose and with quality = "GOOD". The derived evening "Best PEF" for the statistical analysis will be calculated only for evening sessions recorded pre-dose (see section 4.1.12) and with at least two PEF measurements with quality = "GOOD". Baseline for evening PEF will be calculated as the average of all derived evening "Best PEF" values from the evening session of the day of Visit 1 to the evening session of the day before Visit 2 (inclusive). Standard rounding to the nearest integer will be applied. The baseline will be calculated if at least 7 derived evening "Best PEF" values will be available during the run-in period. The derived evening "Best PEF" value will be considered in the calculation.
Average use of rescue medication	A day will be constituted by the data recorded in the evening session of that day plus the data recorded in the morning session of the next day. For each day, the "daily use of rescue medication" will be calculated as the sum of the number of puffs taken during the day (recorded in the PM session of the day - Q6 for run-in questionnaire) and taken during the night (recorded in the AM session of the next day - Q8 for run-in questionnaire). If one of the two sessions (evening or morning) associated with the day is missing, the daily use of rescue medication in that day will be calculated using the available session only. Baseline for average use of rescue medication will be calculated as the mean of the daily use of rescue medication of the data recorded from the evening session of the day of Visit 1 to the morning session of the day of Visit 2 (inclusive). Standard rounding to two decimal places will be applied. The baseline will be calculated if at least 7 daily use of rescue

	medication will be available on the data of the run-in period.
Percentage of rescue medication-free days	A rescue medication-free day is a day with daily use of rescue medication = 0. Baseline of percentage of rescue medication-free days will be calculated as follows: Baseline of percentage of rescue medication-free days = (number of rescue medication-free days during run-in period / number of days with available daily use of rescue medication during run-in period)*100. With number of rescue medication-free days during run-in period and number of days with available daily use of rescue medication during run-in period calculated on the data recorded from the evening session of the day of Visit 1 to the morning session of the day of Visit 2 (inclusive). A minimum of 7 days with available daily use of rescue medication will be required in the run-in period to consider the baseline of percentage of rescue medication-free days as non-missing.
Total Daily asthma symptoms score	Symptoms to be considered are cough, wheeze, chest tightness, breathlessness. A day will be constituted by the data recorded in the evening session of that day plus the data recorded in the morning session of the next day. For each day of run-in period, the "daily symptoms score" will be calculated as the mean of the 8 scores (i.e., 4 PM symptoms scores of the day (Q2-Q5) and 4 AM symptoms scores of the next day (Q3-Q6)). Standard rounding to two decimal places will be applied. If one of the two sessions (evening or morning) associated with the day is missing, the daily symptom score will be calculated on the available session only. Baseline daily symptoms score will be calculated as the mean of the daily symptoms score of the data recorded from the evening session of the day of Visit 1 to the morning session of the day of Visit 2 (inclusive). Standard rounding to two decimal places will be applied. The baseline will be calculated if at least 7 daily symptoms scores will be available on the data of the run-in period.
Daily asthma symptom score of each symptom (cough, wheeze, chest tightness, breathlessness)	A day will be constituted by the data recorded in the evening session of that day plus the data recorded in the morning session of the next day. For each day of run-in period, the "daily symptom score" will be calculated as the mean of the 2 scores (i.e., 1 PM symptom score of the day and 1 AM symptom score of the next day). Standard rounding to two decimal places will be applied. If one of the two sessions (evening or morning) associated with the day is missing, the daily symptom score will be calculated on the available session only (the symptom score of the available

	session will be taken). Baseline daily symptom score will be calculated as the mean of the daily symptom score of the data recorded from the evening session of the day of Visit 1 to the morning session of the day of Visit 2 (inclusive). Standard rounding to two decimal places will be applied. The baseline will be calculated if at least 7 daily symptom scores will be available on the data of the run-in period.
Overall night-time asthma symptoms score	A day will be constituted by the data recorded in the morning session of the next day. For each day of run-in period, the "overall night-time symptoms score" will be the overall morning symptoms score of the next day (Q2 in the AM session of run-in questionnaire). Baseline overall night-time symptoms score will be calculated as the mean of the overall night-time symptoms score of the data recorded from the morning session of the day after Visit 1 to the morning session of the day of Visit 2 (inclusive). Standard rounding to two decimal places will be applied. The baseline will be calculated if at least 7 overall night time symptoms score will be available on the data of the run-in period.
Percentage of asthma symptom-free days	An asthma symptom-free day is a day with total daily asthma symptom score = 0. Baseline of percentage of asthma symptom-free days will be calculated as follows: Baseline of percentage of asthma symptom-free days = (number of asthma symptom-free days during run-in period / number of days with available total daily asthma symptom score during run-in period)*100. With number of asthma symptom-free days during run-in period and number of days with available total daily asthma symptom score during run-in period calculated on the data recorded from the evening session of the day of Visit 1 to the morning session of the day of Visit 2 (inclusive). A minimum of 7 days with available total daily asthma symptom score will be required in the run-in period to consider the baseline of percentage of asthma symptom-free days as non-missing.
Percentage of asthma control days	An asthma control day is a day with total daily asthma symptom score = 0 and daily use of rescue medication = 0. Baseline of percentage of asthma control days will be calculated as follows: Baseline of percentage of asthma control days = (number of asthma control days / number of days with available total daily asthma symptom score and daily use of rescue medication)*100. With number of asthma control days and number of days with available total daily asthma symptom score and daily use of

	rescue medication calculated on the data recorded from the evening session of the day of Visit 1 to the morning session of the day of Visit 2 (inclusive). A minimum of 7 days with available both total daily asthma symptom score and daily use of rescue medication will be required in the run-in period to consider the baseline of percentage of asthma control days as non-missing.
Pre-dose FVC	Baseline for pre-dose FVC will be calculated as average of the highest FVC measurements (L) from the V2Pre45min & V2Pre15min. If one of the two pre-dose values is missing, the baseline will be equal to the available pre-dose value.
Pre-dose IC and VC	Baseline will be the IC and VC measured at Visit 2, pre-dose (V2Pre45min).
Vital signs	Baseline for vital signs (SBP and DBP) will be the measurement at Visit 2, pre-dose.
Change from baseline in pre-dose 12-lead ECG parameters Change from baseline in post-dose 12-lead ECG parameters	Baseline for change from baseline in pre-dose/post-dose 12-lead ECG parameters will be the measurement at Visit 2, pre-dose.
24-hour Holter ECG: Change from baseline in 24-hour average HR	Baseline for change from baseline in 24-hour average HR will be the 24-hour average HR at Visit 2, pre-dose (from the 24-hour Holter ECG recording starting a day before Visit 2 and ending pre-dose at Visit 2) In case of 24-hour Holter ECG at Visit 2 including an end date time after the administration date time: Baseline in 24-hour average HR will be re-calculated using all hourly sessions having an end time before the first administration time. HR of each hourly session will be weighted by the real duration of the hour session in minute

4.1.7 Visit dates

For each visit, the date recorded by the Investigator in the eCRF (variable SVSTDTC in the SDTM SV domain) 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 date of first randomised study medication intake considering the eCRF. This date corresponds to the date part of the variable RFSTDTC in the SDTM dataset DM.

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

4.1.9 Date of Start of Randomised Treatment Period

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 randomised patients who received at least one dose of the study treatment;
- the date of Visit 2 for patients randomised, but not treated.

The need for deviations from this rule in single cases will be evaluated during the blind data review and documented in the Data Review Report.

4.1.10 Data Re-allocation

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

- Data collected at multiple visits (spirometry, ACQ-7, health economic data, vital signs, ECG, Holter and laboratory data) and recorded at the study termination visit for discontinued patients will be re-allocated by selecting the planned theoretical visit following the last one performed before the study termination visit with the expected theoretical 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 planned theoretical Visit 5, 6 or 7 depending on the date of the study termination visit. If the study termination visit is equidistant between two planned theoretical visits, data will be reallocated to the latest of the two possible planned theoretical visits. 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:
    - laboratory data can be re-allocated only to Visits 5 and 7;
    - Holter data can be re-allocated only to Visits 4, 5 and 7;
- for discontinued patients, efficacy data recorded in the diaries from the last visit performed before the study termination visit or the date of discontinuation onwards will be reallocated to the next expected inter-visit period;
- for discontinued patients, study medication intake data recorded in the diaries from the last visit performed before the date of last randomised study medication intake onwards will be reallocated to the next expected inter-visit period;

- in case of missing intermediate visit not due to the re-allocation of data collected at the study termination visit (e.g., Visit 4 missing, but Visits 3 and 5 performed), an expected date for the missing visit will be imputed in order to define the inter-visit periods for diary data. The expected date for the missing visit will be imputed as follows:
    - Visit 3 expected date = Visit 2 date + 28 days;
    - Visit 4 expected date = Visit 2 date + 84 days;
    - Visit 5 expected date = Visit 2 date + 182 days;
    - Visit 6 expected date = Visit 2 date + 280 days.

The following general rules to handle unscheduled/optional assessments will be considered:

- 12-lead ECG:
    - in case of multiple 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;
    - at Visit 1 and Visit 2, the assessments originally flagged as "VISIT 1" and "VISIT 2" – "PREDOSE", respectively, will always be used also in case of additional measurements. The rationale for this exception is that the original values were considered for the assessments of eligibility.
- laboratories: the last assessment before the date of first randomised study medication intake of each parameter will 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 the first randomised study medication intake will be considered in the analysis. If no complete assessment is available, the last assessment before date of first randomised study medication with the highest number of available parameters will be considered in the analysis.

Potential issues of the approach above defined and other decisions regarding data re-allocation will be evaluated during the blind review of the data and documented in the Data Review Report.

Note: All the analyses (descriptive, inferential including Multiple Imputation) will be performed after this re-allocation of data.

4.1.11 Diary Data

The data recorded in the diaries after min(date of completion/discontinuation, date of Visit 7 or study termination visit) will not be considered in the calculation of compliance and of the efficacy variables.

In case of duplicate diary data (more than one set of answers for the same day) the set of answers entered first will be considered in the analysis.

Regarding the diary data recorded twice a day, in case of more than one session with same day and same time point (e.g. daytime), the set of answered entered first will be considered in the analysis.

4.1.12 Exclusion of Data from the Statistical Analysis

Spirometry parameters:

All spirometry data not rejected by the Investigator will be considered in the statistical analysis, even those classified as "rejected" by the over-reader. This follows the approach recommended by the paper by Hankinson et al. (Eur Respir J 2015), where it was concluded that quality assessment regarding the acceptability of individual blows should be primarily used as an aid to assess good quality during testing rather than a reason to subsequently disregard data.

Daily PEF measurements:

All PEF values lower than 50 L/min or upper than 900 L/min will be excluded from the analysis datasets, since they are considered not reliable by Vitalograph [5], for the patient population included in the study.

The 'best' PEF derived and recorded in the diary data will not be used as only sessions with at least two good pre-dose PEF measurements will be considered for the statistical analysis.
Knowing that the pre-dose is defined respectively for the morning and evening PEF as:

- For morning PEF:
  PEF measurements done prior any pMDI inhalation for CHF 5993 pMDI HS and CHF 1535 pMDI HS treatment arms and before any pMDI and Spiriva Respimat inhalation for CHF 1535 pMDI HS + Tiotropium treatment arm
- For evening PEF:
  PEF measurements done prior any pMDI inhalation for CHF 5993 pMDI HS and CHF 1535 pMDI HS treatment arms and before any pMDI.

Therefore a new 'best' PEF will be derived by taking the highest PEF value from all PEF measurements recorded pre-dose and with quality = "GOOD". This new 'best' PEF will be calculated only for sessions with at least two PEF measurements recorded pre-dose and with quality = "GOOD".

Holter data and 12-lead ECG parameters:

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

- Patients with a pacemaker inserted before study entry will be identified by the presence of at least one of the following Preferred Terms in the medical/surgical history or concomitant diseases: "Cardiac pacemaker battery replacement", "Cardiac pacemaker evaluation", "Cardiac pacemaker insertion", "Cardiac pacemaker replacement", "Electrocardiogram pacemaker spike", "Pacemaker generated arrhythmia", "Pacemaker generated rhythm", "Pacemaker syndrome", "Cardiac assistant device user".

- Patients with a pacemaker inserted during study will be identified by the presence of the Preferred Term "Cardiac pacemaker insertion" in the procedures (other relevant cases may be identified in the Data Review Report). In these cases, data will be excluded from the analysis from the day of pacemaker insertion onwards.
- Patients with atrial fibrillation will be identified by the presence of at least one of the following Preferred Terms in the concomitant diseases: "Atrial fibrillation", "Cardiac fibrillation".

At each time point, 12-lead ECG parameters will be also excluded from the statistical analysis if PR = 0 (since this is an indication of an unreliable ECG).

Holter recordings with a duration of the analysed period <18 hours will be excluded from the statistical analysis.

At Visit 2, in case Holter recording stop date time is after the study medication intake date time, Visit 2 Holter data will be excluded from the statistical analysis. The only exception will regard the HR parameters (HR average, HR minimum and HR maximum) and associated analysed duration which will be re-calculated using all hourly session having an end date time before the study medication intake date time.

For each Holter recording, atrial fibrillation peak average rate (bpm) and time in atrial fibrillation percentage will be included in the analysis only if atrial fibrillation peak average rate > 0. Since both these parameters are set to 0 in the results of Holter recordings if no atrial fibrillation occurred, this rule will avoid patients with no atrial fibrillation to be included in the analysis of parameters related to this abnormality.

In case of data excluded from the statistical analysis (in all situations above described in this paragraph but also in other cases, for example: spirometry tests excluded due to technical issues, 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 baseline measurement is excluded. In the responder analysis, values excluded from the analysis will be considered as missing values.

4.1.13 Spirometry and ACQ-7 score at Visit 1

If the spirometry was repeated before Visit 2 (at Visit 1.1), the 2nd assessment will be considered as the Visit 1 assessment in all the analyses. This rule will be applied irrespective of the answer provided to inclusion criterion no. 6 at Visit 1. Data transferred from eRT (referring to these data as the "centralised spirometry data") and not eCRF data will be used.

The same approach will apply to ACQ-7 score, irrespective of the answer provided to inclusion criterion no. 7 at Visit 1. Therefore, if the spirometry was repeated at Visit 1.1, the ACQ-7 score reassessed at the re-scheduled visit will be considered as the Visit 1 assessment in all the analyses.

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.

4.2 Interim Analysis

No interim analysis is planned for this study.

4.3 Disposition of Patients

The number of patients screened, the number of screen failures and the number of patients with each reason for screen failure will be presented (overall). All patients will be included.

The number of patients randomised at Visit 2, who attended Visits 3, 4, 5 and 6, who completed Visit 7 and who discontinued and performed Early Termination visit will be presented by treatment group using the Randomised population.

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

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.

Time to discontinuation from the study after randomisation will be analysed using the Kaplan-Meier method for the Randomised population. For the study periods [0-4) weeks, [4-12) weeks, [12-26) weeks, [26-40) weeks, [40-52) weeks and [52 weeks-End of Treatment (EoT)], the number of patients in study at the beginning of the period, the cumulative number of discontinued patients at the end of the period and the probability of discontinuation at the end of the period with the associated 95% confidence intervals (CIs) will be presented by treatment group. Plot of time to discontinuation by treatment group will also be presented. A comparison between treatments will also be performed by means of the log-rank test.

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

The number of patients included in each of the Randomised, Safety, ITT, PP populations and in the Holter subset will be summarised for each treatment group and overall. The summary will also be presented by region and country within region. Where region = country, data will be reported only once in the table (at the "region" level).

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 the 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.

4.4.1 Demography/Baseline Characteristics

Demographic and baseline characteristics will be summarised by treatment group and overall. This will include age, age in class (<65, ≥65 years), sex, race, height, weight, BMI and BMI class (< 25, [25-30), ≥ 30 kg/m^2). Separate summaries will be produced using the randomised, Safety, ITT, and PP populations. The same summary will be also presented stratifying by inclusion in the Holter subset using the Safety population.

4.4.2 Smoking Status

Smoking status (ex-smoker or non-smoker), duration of smoking (years) and number of pack-years recorded at Visit 1 will be presented by treatment group and overall on Safety, ITT, PP populations.

Notes:

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

4.4.3 Asthma History

Duration of asthma disease (years), duration of asthma disease by class (< 5, [5-20), ≥ 20 years), asthma medication category at study entry (fixed ICS/LABA combination or free ICS+LABA combination), before study entry, spacer device use during study, number of asthma exacerbations in the previous year [as a continuous and categorical variable (0, 1, 2, 3, >3) ; the category "0" will not be presented if all patients had at least 1 asthma exacerbation in the previous year, as per eligibility criteria] and time since last documented asthma exacerbation (months) will be presented by treatment group and overall. Separate summaries will be produced using the Safety, ITT and PP populations.

Notes:

- Spacer device use before Study Entry will be based on the "Asthma History" form of the eCRF;
- Spacer device use during study will be based on the "Run-In Drug Administration" and the "Study Medication Administration" forms of the eCRF (use of "AeroChamber Plus"). In case of changes in spacer use during the study, a patient will be considered as a spacer user during study if the spacer was used for >50% of the duration of the randomised treatment period (i.e., from the start of the randomised treatment period – see section 4.1.9 - up to completion/discontinuation) of the patient. In order to perform this evaluation, the following rules will be considered:
    - in each inter-visit period visit x – visit y, the spacer will be considered used if used at visit y;
    - in case of discontinuation:

  - if no early termination visit was performed, the spacer will be considered used in the period from the last visit performed to discontinuation if used at the last visit performed;
  - if an early termination visit with no intake of the study medication was performed, the spacer will be considered used in the period from the last visit before early termination visit to discontinuation if used at the last visit before early termination visit;
  - if an early termination visit with intake of the study medication was performed, the usual rule for inter-visit periods applies.
- Duration of asthma disease (years) will be calculated as (date of Visit 1 – date of first asthma diagnosis)/365.25;
- Time since last documented asthma exacerbation (months) will be calculated as (date of Visit 1 – date of last documented asthma 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:

- Visit 1: FEV_1 (L), FEV_1 % of predicted normal value, FVC (L) pre-salbutamol intake; FEV_1 (L), FEV_1 % of predicted normal value, FVC (L) post-salbutamol intake; reversibility in FEV_1 (mL) [as a continuous and categorical variable (delta FEV_1: (200-400], > 400 mL)], reversibility in FEV_1 (%);
- Visit 2: FEV_1 (L), FEV_1 % of predicted normal value, FVC (L), IC (L) and VC (L) pre-dose. For FEV_1 (L and % of predicted normal value) and FVC, the mean of pre-dose (45 min and 15 min pre-dose) values will be summarised.

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

4.4.5 ACQ-7 questionnaire

The ACQ-7 score at Visit 1 and Visit 2 will be summarised by treatment group and overall using the ITT population.

4.4.6 PEF, use of rescue medication and asthma symptoms scores

Average morning and evening PEF, average use of rescue medication, percentage of rescue medication-free days, average daily asthma symptoms scores (total asthma symptoms score, cough symptom score, wheeze symptom score, chest tightness symptom score, breathlessness symptom score, overall night-time asthma symptoms score), percentage of asthma symptom-free days and percentage of asthma control days at baseline will be summarised by treatment group and overall using the ITT population.

For baseline definition, please refer to the

Table 1: Baseline **calculations**.

4.4.7 Medical/Surgical History and Concomitant Diseases

Medical/surgical history and concomitant diseases will be summarised by SOC and preferred term (PT), by treatment group and overall. Separate summaries will be produced using the Safety and ITT populations.

Notes:

- Medical/surgical history and concomitant diseases (other than asthma) will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 18.1;
- 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, concomitant medications and post-study medications will be summarised by treatment group and overall (except for concomitant and post-study 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 Preferred Name.

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 < min(date of completion/discontinuation, date of Visit 7 or study termination visit);
- post-study medication: start date ≥ min(date of completion/discontinuation, date of Visit 7 or study termination visit).

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 the table below:

Common name	Preferred Names
“SALBUTAMOL”	“SALBUTAMOL” “SALBUTAMOL SULFATE”
“TERBUTALINE”	“TERBUTALINE” “TERBUTALINE SULFATE”
“FENOTEROL”	“FENOTEROL” “FENOTEROL HYDROBROMIDE”
“SALMETEROL”	“SALMETEROL” “SALMETEROL XINAFOATE”
“FORMOTEROL”	“FORMOTEROL” “FORMOTEROL FUMARATE”
“INDACATEROL”	“INDACATEROL” “INDACATEROL MALEATE” “INDACATEROL XINAFOATE” “INDACATEROL ACETATE”
“OLODATEROL”	“OLODATEROL” “OLODATEROL HYDROCHLORIDE”
“FLUTICASONE W/SALMETEROL”	“FLUTICASONE W/SALMETEROL (FLUTICASONE,SALMETEROL)” “SERETIDE (FLUTICASONE PROPIONATE,SALMETEROL XINAFOATE)” “FLUTICASONE PROPIONATE W/SALMETEROL (FLUTICASONE PROPIONATE,SALMETEROL)”
“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)”
“BECLOMETASONE W/SALBUTAMOL”	“CLENIL COMPOSITUM /00548601/ (BECLOMETASONE DIPROPIONATE,SALBUTAMOL)”
“FLUTICASONE W/VILANTEROL”	“FLUTICASONE FUROATE W/VILANTEROL (FLUTICASONE FUROATE,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)”
“ACLIDINIUM W/FORMOTEROL”	“ACLIDINIUM BROMIDE W/FORMOTEROL FUMARATE”
“UMECLIDINIUM W/VILANTEROL”	“UMECLIDINIUM W/VILANTEROL” “UMECLIDINIUM BROMIDE W/VILANTEROL TRIFENATATE”
“BECLOMETASONE”	“BECLOMETASONE” “BECLOMETASONE DIPROPIONATE” “BECLOMETASONE DIPROPIONATE MONOHYDRATE” “BECLOMETASONE SALICYLATE” “BECLOMETASONE PROPIONATE”
“FLUTICASONE”	“FLUTICASONE” “FLUTICASONE PROPIONATE” “FLUTICASONE FUROATE”
“MOMETASONE”	“MOMETASONE” “MOMETASONE FUROATE” “MOMETASONE FUROATE MONOHYDRATE”
“IPRATROPIUM”	“IPRATROPIUM” “IPRATROPIUM BROMIDE” “IPRATROPIUM BROMIDE MONOHYDRATE”
“TIOTROPIUM”	“TIOTROPIUM” “TIOTROPIUM BROMIDE” “TIOTROPIUM BROMIDE MONOHYDRATE”
“ACLIDINIUM”	“ACLIDINIUM” “ACLIDINIUM BROMIDE”
“GLYCOPYRRONIUM”	“GLYCOPYRRONIUM” “GLYCOPYRRONIUM BROMIDE”
“UMECLIDINIUM”	“UMECLIDINIUM” “UMECLIDINIUM BROMIDE”
“MONTELUKAST”	“MONTELUKAST” “MONTELUKAST SODIUM”

The following tables will be provided:

- previous medications and medications maintained during the randomised treatment period:
    - Asthma medications including medications for asthma exacerbation;
    - non-asthma medications;
- concomitant medications:
    - Asthma medications not including medications for asthma exacerbation;
    - medications for asthma exacerbation;
    - non-asthma medications;
- post-study medications.

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

The rules to identify asthma medications (administered for asthma exacerbations and for other reasons) will be agreed during the blind data review meetings. The following rules are currently proposed for selecting medications (these may be amended during the blind data review meetings and any such amendments will be fully documented in the Data Review Report):

Previous medications and medications maintained during the randomised treatment period:

Asthma Medications

Any medications with an indication containing the term 'ASTHMA'.

Concomitant medications and post-study medications:

Asthma Medications not including medications for asthma exacerbations

Any medications with an indication containing the term 'ASTHMA', excluding medications for asthma exacerbations (see the following definition).

Medications for Asthma Exacerbations

Any medications with an indication containing the term 'AE: ASTHMA EXACERBATION'.

Medications taken for asthma exacerbation during the study period will be associated to the number of the corresponding asthma 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 blind data review meetings in order to define the appropriate association.

Notes:

- Medications are coded using the World Health Organisation (WHO) Drug Dictionary B2 enhanced, version September 2015;

- 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, concomitant and post-study procedures will be summarised by treatment group and overall for the ITT population through frequency distributions and percentages by SOC and PT.

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 < min(date of completion/discontinuation, date of Visit 7 or study termination visit).;
- post-study procedures: start date ≥ min(date of completion/discontinuation, date of Visit 7 or study termination visit).

Notes:

- Procedures are coded using MedDRA version 18.1.

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.

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 by treatment group and overall using the Safety population. A patient will be classed as having a pacemaker according to the rule defined in section 4.1.12.

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

4.4.12 24-hour Holter ECG at Visit 1 and Visit 2

The following variables obtained from the 24 h Holter evaluation at Visit 1 and Visit 2 will be summarised by treatment group and overall using the Holter subset:

- Average HR (bpm);
- Minimum HR (bpm);
- Maximum HR (bpm);
- Longest Tachycardia Duration (min);

- Longest Tachycardia Maximum HR (bpm);
- Fastest Tachycardia Duration (min);
- Fastest Tachycardia Maximum HR (bpm);
- Longest Bradycardia Duration (min);
- Longest Bradycardia Minimum HR (bpm);
- Slowest Bradycardia Duration (min);
- Slowest Bradycardia Minimum HR (bpm);
- Time in Atrial Fibrillation Percentage;
- Atrial Fibrillation Peak Average Rate (bpm);
- Supraventricular Total;
- Ventricular Total;
- RR > 2 sec (yes/no: yes if number of RR > 2 sec > 0, no if number of RR > 2 sec = 0).

4.5 Treatment Compliance

In general, treatment compliance will be evaluated on the basis of 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 scheduled clinic visits), the eCRF data will be considered.

For patients with an incorrect setting of electronic diary at randomisation (questions on run-in medication asked during the randomised treatment period or vice versa), the calculation of extent of exposure will not be modified, but the number of scheduled and administered dose and the compliance will be calculated only on the sessions with the correct question on the medication. This means that the number of scheduled and administered doses and the treatment compliance will be calculated:

- in case of incorrect questions during the run-in period, up to last session before the evening session of the day of Visit 2 with no incorrect questions (considering also the missing sessions);
- in case of incorrect questions during the randomised treatment period, from the evening session of the day of the first randomised study medication intake with no incorrect questions (considering also the missing sessions).

The above rules will be applied to patients switching from the questions on run-in medication to the ones on the correct randomised study medication only once. The handling of more complex cases (i.e., with more than one switch or with questions on the incorrect randomised treatment arm) will be defined in the Data Review Report.

4.5.1 Run-in Period

Treatment exposure (days) will be calculated with the following formula: date of last run-in study medication intake – date of first run-in study medication intake +1.

The date of first and last run-in study medication intake will be derived on the basis of the information recorded on the diary and the eCRF. For the date of last run-in study medication intake, diary data will be considered up to up to the day before start of randomised treatment period (this limit is required in order to handle cases with questions on run-in medication incorrectly asked during the randomised treatment period).

The evaluation of the compliance during the run-in period will be based on the following formula:

Compliance (%) = (# Administered Doses / # Scheduled Doses)*100.

The total number of administered doses will be calculated as the total number of inhalations recorded from the evening session of the day of Visit 1 to the morning session of the day of start of randomised treatment period (reporting the dose taken the evening before), inclusive.

The total number of scheduled doses will be calculated using the following formula:

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

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

- [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) will be calculated with the following formula: date of last randomised study medication intake - date of first randomised study medication intake + 1.

The handling of cases of missing or partial date of last randomised study medication intake, will be defined in the Data Review Report.

The evaluation of the compliance during the randomised treatment period will be based on the following formula:

Compliance (%) = (# Administered Doses / # Scheduled Doses)*100.

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

Depending of the study drug administered, the total number of scheduled doses will be calculated using the following formula:

- For CHF 5993 pMDI HS and CHF 1535 pMDI HS:
    - # scheduled doses = Extent of exposure (days)*4 (2 inhalations pMDI b.i.d.).

  If the last day considered in the formula is the day of Visit 7 (date of last randomised study medication intake = Date of Visit 7), the number of scheduled doses on this day will be 2 (2 inhalations) as study medication will be administered only in the morning. Therefore the total number of scheduled doses will be:

    - (Date of last randomised study medication intake - Date of first randomised study medication intake)*4 + 2.

  The information on study medication intake on that day will be taken from the eCRF.

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

    - # scheduled doses = 2 (2 inhalations);
    - the information on study medication intake will be taken from the eCRF.

- For CHF 1535 pMDI HS + Tiotropium:
    - # scheduled doses = Extent of exposure (days)*6 (2 inhalations pMDI b.i.d. + 2 inhalations Respimat o.d).

  If the last day considered in the formula is the day of Visit 7 (date of last randomised study medication intake = Date of Visit 7), the number of scheduled doses on this day will be 4 (2 inhalations pMDI + 2 inhalations Respimat) as study medication will be administered only in the morning. Therefore the total number of scheduled doses will be:

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

  The information on study medication intake on that day will be taken from the eCRF.

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

    - # scheduled doses = 4 (2 inhalations pMDI + 2 inhalations Respimat)
    - the information on study medication intake will be taken from the eCRF.

The approach above defined for the calculation of compliance during the randomised treatment period assumes no intake of the study medication in case of missing data.

A range of 65-135% will be taken into account for a satisfactory level of compliance.

Descriptive summaries of treatment compliance (%) will be presented by treatment group for the randomised treatment period using the Safety and ITT populations. An additional summary displaying the number and percentage of patients in the same categories of compliance above defined for the run-in period will also be presented by treatment group.

In addition, treatment compliance during the randomised treatment period will also be presented for the following categories: <65%, ≥65% and ≤135%, >135%.

4.5.3 Inter-Visit Periods

Of note, all the definitions included in the table below and used in this section are expressed in terms of planned sessions. For example, the first session to be considered in inter-visit period Visit 2 – Visit 3 will be always the evening session of the day of first randomised study medication intake, irrespective of the availability of this specific session.

Inter-visit period visit i - visit i+1 ($2 \leq i \leq 6$)	
First session of the period	Last session of the period
• If i=2 then first session = evening session of day of first randomised study medication intake. • Else first session = evening session of day 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 last session = morning session of day of visit *i+1* • Else: o For completed patients: last session = study medication intake recorded at Visit 7; o For discontinued patients: last session = the last session of the day of last randomised study medication intake.

Data recorded from the first session of the period to the last session of the period will be considered as data of the inter-visit period.

Treatment exposure (days) during each inter-visit period will be calculated with the following formula: date of last session of the inter-visit period – date of first session of the inter-visit period.

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

- Compliance (%) = (# Administered Doses / # Scheduled Doses)*100.

Depending of the study drug administered, the total number of scheduled doses during each inter-visit period will be calculated using the following formula:

- For CHF 5993 pMDI HS and CHF 1535 pMDI HS:
    - # scheduled doses = Extent of exposure during inter-visit period (days)*4 (2 inhalations b.i.d.).

For the last inter-visit period of each patient:

Condition	Treatment exposure (days) during last inter-visit period	Total number of scheduled doses for last inter-visit period
• If the last day considered in the formula is the date of a scheduled visit (date of last randomised study medication intake = date of a scheduled Visit), so the number of scheduled puffs on this day will be 2 (2 inhalations) as study medication will be administered only in the morning. The information on study medication intake on that day will be taken from the eCRF; • If the last session considered in the formula is an evening session (for discontinued patients only).	date of last session of the period – date of first session of the period + 1	(date of last session of the period – date of first session of the period)*4 + 2
• If the last session considered in the formula is a morning session (for discontinued patients only).	date of last session of the period – date of first session on the period *NB : date of last session of the period = date of last randomised study medication intake + 1*	(date of last session of the period – date of first session of the period)*4 *NB :date of last session of the period = date of last randomised study medication intake + 1*

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

- treatment exposure = 1 day;
- # scheduled doses = 2 (2 inhalations);
- the information on study medication intake will be taken from the eCRF.

- For CHF 1535 pMDI HS + Tiotropium:
  - # scheduled doses = Extent of exposure during inter-visit period (days)*6 (2 inhalations pMDI b.i.d. + 2 inhalations Respimat o.d).

For the last inter-visit period of each patient:

Condition	Treatment exposure (days) during last inter-visit period	Total number of scheduled doses for last inter-visit period
• If the last day considered in the formula is the date of a scheduled visit (date of last randomised study medication intake = date of a scheduled Visit), so the number of scheduled puffs on this day will be 4 (2 inhalations pMDI + 2 inhalations Respimat) as study medication will be administered only in the morning. The information on study medication intake on that day will be taken from the eCRF; • If the last session considered in the formula is an evening session (for discontinued patients only).	date of last session of the period – date of first session of the period + 1	(date of last session of the period – date of first session of the period)*6 + 4
• If the last session considered in the formula is a morning session (for discontinued patients only).	date of last session of the period – date of first session on the period *NB: date of last session of the period = date of last randomised study medication intake + 1*	(date of last session of the period – date of first session of the period)*6 *NB: date of last session of the period = date of last randomised study medication intake + 1*

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

- treatment exposure = 1 day;
- # scheduled doses = 4 (2 inhalations pMDI + 2 inhalations Respimat);
- the information on study medication intake will be taken from the eCRF.

For patients with an incorrect setting of electronic diary at randomisation (questions on run-in medication asked during the randomised treatment period), the compliance will be calculated only on the days with the correct question on the medication.

Descriptive summaries of treatment compliance will be presented by treatment group for each inter-visit period using the Safety and ITT populations.

4.6 Diary Compliance

Compliance to the use of diaries (run-in and randomised treatment periods) will be summarised using the ITT population.

4.6.1 Run-in Period

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

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

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

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

- [0%-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

Sessions recorded from the evening of the date of start of randomised treatment period to min(date of completion/discontinuation, date of Visit 7 or study termination visit) will be considered as data of the randomised treatment period.

The following formula will be used:

- Compliance during the randomised treatment period (%) = [Total number of sessions in the randomised treatment period with data recorded in the diaries / (2*(min(date of completion/discontinuation, date of Visit 7 or study termination visit) – Date of start of randomised treatment period) + 1)]*100.

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

4.7 Efficacy Analysis

The comparisons between CHF 5993 pMDI HS and CHF 1535 pMDI HS will be conducted according to a hierarchical testing procedure to test the co-primary and key secondary endpoints in the following order:

1. Change from baseline in pre-dose FEV_1 at Week 26 and Moderate and Severe asthma exacerbation rate over 52 weeks (see sections 4.7.1.1 and 4.7.1.2);
2. Change from baseline in peak FEV_1 at Week 26 (see section 4.7.2.1);
3. Change from baseline in morning PEF over Week 26 (see section 4.7.2.2);
4. Severe asthma exacerbation rate over 52 weeks in the pooled analysis (see section 4.7.2.3);

At step 1, both superiority tests on the two co-primary endpoints must be significant. At each of the next steps of the procedure, no confirmatory claims will be made unless the superiority of CHF 5993 pMDI HS over CHF 1535 pMDI HS in all the preceding steps will be demonstrated.

4.7.1 Co-primary Efficacy Variables

The co-primary efficacy variables are:

- Change from baseline in pre-dose FEV_1 at Week 26
- Moderate and Severe asthma exacerbation rate over 52 weeks

4.7.1.1 Change from Baseline in Pre-dose FEV_1 at Week 26

Since the analysis of change from baseline in pre-dose FEV_1 at Week 26 is based on the same statistical model used for the analysis of change from baseline in pre-dose FEV_1 at all the other clinical visits, details on these secondary efficacy variables are also provided in this section.

The pre-dose FEV_1 at a visit is the mean between the available measurements at 45 min and 15 min pre-dose.

For Baseline pre-dose FEV_1, please refer to the

Table 1: Baseline calculations.

Pre-dose FEV_1 values at each visit will be summarised by treatment group using descriptive statistics. Changes from baseline at each visit will also be summarised by treatment group. In order to provide a comprehensive description of the results on this parameter, the post-dose FEV_1 values and their changes from baseline will be included in this summary table as well.

The above summary will be performed using the ITT and PP populations.

Change from baseline in pre-dose FEV_1 will be analysed using a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country as fixed effects, and baseline value and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed and the Kenward-Roger adjustment will be used for the degrees of freedom.

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

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

Superiority of CHF 5993 pMDI HS over CHF 1535 pMDI HS will be demonstrated if the lower limit of the confidence interval for the adjusted mean difference between CHF 5993 pMDI HS and CHF 1535 pMDI HS at Week 26 pMDI is >0.

The adjusted mean differences between CHF 5993 pMDI HS and CHF 1535 pMDI HS + Tiotropium and their 95% CIs will be estimated for descriptive purposes.

Similarly, the adjusted mean differences between CHF 1535 pMDI HS + Tiotropium and CHF 1535 pMDI HS and their 95% CIs will be also estimated for descriptive purposes.

The above comparisons 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 mixed model will also be provided.

The above analysis will be performed using the ITT and PP populations.

In order to assess the potential impact of missing data on the results of the co-primary efficacy analysis, the following sensitivity analyses based on multiple imputation (MI) will be performed on all randomised patients. In a preliminary step, imputation based on the missing at random (MAR) assumption will be performed using the joint modelling approach in order to obtain monotone missing data patterns. The imputation will be performed considering the following variables: treatment, country, pre-bronchodilator FEV_1 value at Visit 1, pre-dose FEV_1 values from Visit 2 to Visit 7. Then, a regression-based imputation will be performed according to the following strategies:

- missing at random: imputation based on the MAR assumption in all treatment groups. The imputation model will correspond to the one used in the preliminary step. This analysis is based on the same assumption behind the MMRM used for the primary efficacy analysis, however it will allow the inclusion in the analysis of all randomised patients (this is not always possible with the MMRM);
- copy reference: imputation based on the data distribution of the CHF 5993 pMDI HS group in all treatment groups. The imputation model will correspond to the one used in the preliminary step, except for the exclusion of the treatment effect. This analysis mimics the case where discontinued patients in the CHF 1535 pMDI HS and CHF 1535 pMDI HS + Tiotropium arms are switched to the treatment with CHF 5993 pMDI HS (expected to be more effective than CHF 1535 pMDI HS and comparable to CHF 1535 pMDI HS + Tiotropium);
- baseline observation carried forward (BOCF) – like: imputation based on the distribution of baseline value in all treatment groups. The imputation model will include the following variables: country, pre-bronchodilator FEV_1 value at Visit 1.

One thousand imputations will be performed and at each visit the analysis will be based on an ANCOVA model including the following variables: treatment, country as fixed effects, and

baseline value as covariate. Estimates from the models will be then combined using Rubin's rule.

The analysis of pre-dose FEV_1 based on the linear mixed model for repeated measures will be also presented on the ITT population by defined stratification factors described in section 4.1.5.

The adjusted mean differences between treatments at Week 26 (Visit 5) and at Week 52 (Visit 7) and their 95% CIs estimated on the ITT and PP populations, and in the sensitivity and stratified analyses, will be graphically summarised in a forest plot for each comparison between treatments (this means a total of 6 forest plots, one for each visit and treatment comparison).

4.7.1.2 Moderate and Severe asthma Exacerbation Rate over the 52-week treatment period

Moderate and severe asthma exacerbations during the randomised treatment period derived from the Asthma Exacerbations eCRF form will be considered for the analysis.

Only asthma exacerbations with start date ≥ date of start of randomised treatment period and ≤ min(date of completion/discontinuation, date of Visit 7 or study termination visit) will be considered in the analysis. Asthma exacerbations with start date = date of start of randomised treatment period will be discussed case by case during the blind review of the data 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 Data Review Report.

Two asthma exacerbations will be considered as a single episode in the statistical analysis if the second asthma exacerbation started less than 7 days after the end of the previous asthma exacerbation (start date of the next asthma exacerbation - end date of the actual (previous) asthma exacerbation < 7 days). This rule will be applied whatever the severity of the asthma exacerbation (moderate or severe). In case of more than two asthma exacerbations on the same patient, this rule will be applied iteratively (therefore more than two asthma exacerbations may be considered as a single episode). Such cases will be discussed during the blind review of the data and the decisions taken will be documented in the Data Review Report.

The above rule will not apply to the analysis of asthma exacerbations as AEs.

In case of multiple asthma exacerbations considered as a single episode:

- the start date of the first event will be considered as the start date;
- the stop date of the last event will be considered as the stop date;
- a worst-case approach will be considered for the following characteristics of the asthma exacerbation: severity of asthma exacerbation (for example if one of two asthma 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 asthma exacerbation), asthma 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 taking into account the treatments of all the asthma exacerbations to be considered as a single episode (for example if just one of two asthma exacerbations considered as a single episode was treated using systemic corticosteroids, the resulting event will be considered as treated with systemic corticosteroids);
- the total duration of the treatment with systemic corticosteroid and the duration of hospitalisation will be summed. In case of overlapping treatments, each day will be counted only once;
- if the etiologies of the asthma 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 asthma exacerbations considered as a single episode has etiology "Infection" and the other one has etiology "Exposures", the single episode will be considered in the analysis as having multiple etiology "Infection" and "Exposures"). It should be noted that it is already possible for the Investigator to record multiple etiology for each asthma exacerbation. If the etiology is non-missing for at least one of the asthma 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.

As asthma exacerbation will be defined as severe if a treatment with systemic corticosteroids for at least 3 days has been initiated.

As asthma exacerbation will be defined as moderate if fulfilling at least one of the following criteria and leading to a change in treatment:

a) Nocturnal awakening(s) due to asthma requiring SABA for 2 consecutive nights or increase of ≥ 0.75 from baseline in daily symptom score on 2 consecutive days

b) Increase from baseline in occasions of SABA use on 2 consecutive days (minimum increase: 4 puffs/day)

c) ≥ 20% decrease in PEF from baseline on at least 2 consecutive mornings/evenings or ≥ 20% decrease in FEV_1 from baseline

d) Visit to the emergency room/trial site for asthma treatment not requiring systemic corticosteroids

The number and the percentage of patients with moderate/severe asthma exacerbations, the number of moderate/severe asthma 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) = (min(date of completion/discontinuation, date of Visit 7 or study termination visit) - date of start of randomised treatment period + 1) / 365.25.

The rate of moderate/severe asthma 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 asthma exacerbations by the total follow-up time).

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

- Moderate asthma exacerbations;
- Severe asthma exacerbations;
- Asthma exacerbations requiring hospitalisation;
- Asthma exacerbations leading to death.

The number and the percentage of asthma exacerbations treated with systemic corticosteroids will be presented by treatment group.
The total duration of the treatment with systemic corticosteroids will be summarised by treatment group using descriptive statistics and the following categorisations:

- systemic corticosteroids: 1-15 days, 16-30 days, >30 days, Not Evaluable.

An asthma exacerbation will be defined as treated with systemic corticosteroids if this treatment is recorded in the asthma exacerbation form of the eCRF. The duration of the treatment will be evaluated considering the systemic corticosteroids (ATC code H02) associated with the asthma exacerbation.

For each asthma 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, the duration of the treatment with systemic corticosteroids will be classified as “Not Evaluable”.

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

- date of discharge – date of admission + 1.

The duration of the hospitalisation (in days) for asthma exacerbations will be summarised by treatment group using descriptive statistics.

The number of moderate and severe asthma exacerbations during the treatment period will be analysed using a negative binomial model including treatment, Country, number of asthma exacerbations in the previous year (1 or >1), as fixed effects, and log-time on study as an offset. The adjusted asthma exacerbation rates in each treatment group and the adjusted rate ratios with their 95% Wald CIs and p-values will be estimated by the model. Superiority of CHF 5993 pMDI HS over CHF 1535 pMDI HS will be demonstrated if the upper limit of the confidence interval for the adjusted rate ratio between CHF 5993 pMDI HS and CHF 1535 pMDI HS is < 1.

The adjusted rate ratio between CHF 5993 pMDI HS and CHF 1535 pMDI HS + Tiotropium and its 95% CI and p-value will be estimated for descriptive purposes.

Similarly, the adjusted rate ratio between CHF 1535 pMDI HS + Tiotropium and CHF 1535 pMDI HS and its 95% CI and p-value will be also estimated for descriptive purposes.

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 and PP populations.

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

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

Individual rates will be listed only.

In order to assess the potential impact of missing data on the results of the primary efficacy analysis, sensitivity analyses based on multiple imputation (MI) will be performed on all randomised patients based on the approach proposed by Keene et al. [4].

For all patients with a follow-up duration shorter than 365 days (i.e., 52 weeks + 1 day), the number of asthma exacerbations from the end of the follow-up period up to day 365 will be imputed. For the non-treated patients, the follow-up time in years will be calculated using the following formula:

- Follow-up time (years) = [min(date of completion/discontinuation, date of study termination visit) – max(date of randomisation, date of Visit 2) + 1] / 365.25.

The imputation model will include the following variables: treatment, country, number of asthma exacerbations in the previous year. The imputation will be performed according to the following strategies:

- missing at random: imputation based on the MAR assumption in all treatment groups. This analysis is based on the same assumption behind the model used for the primary efficacy analysis, however it will allow the inclusion in the analysis of all randomised patients;
- copy reference: imputation based on the data distribution of the CHF 5993 pMDI HS group in all treatment groups. This analysis mimics the case where discontinued patients in the CHF 1535 pMDI HS and CHF 1535 pMDI HS + Tiotropium arms are switched to the treatment with CHF 5993 pMDI HS (expected to be more effective than CHF 1535 pMDI HS and comparable to CHF 1535 pMDI HS + Tiotropium);

One thousand imputations will be performed and the analysis of the total number of asthma exacerbations (observed + imputed events) will be based on the same negative binomial model used for the primary efficacy analysis. Estimates from the models will be then combined using Rubin's rule.

The analysis of moderate/severe asthma exacerbations based on the negative binomial model will be also performed on the ITT population by defined stratification factors described in section 4.1.5.

The adjusted rate ratios and their 95% CIs estimated on the ITT and PP populations and in the sensitivity and stratified analyses will be graphically summarised in a forest plot

4.7.2 Key Secondary Efficacy Variables

The key secondary efficacy variables are:

- Change from baseline in peak FEV_1 at Week 26 (see section 4.7.2.1);
- Change from baseline in morning PEF over Week 26 (i.e., up to Week 26, see section 4.7.2.2);
- Severe asthma exacerbation rate over 52-week treatment period in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02 (see section 4.7.2.3);

4.7.2.1 Change from baseline in peak FEV_1 at Week 26

Since the analysis of change from baseline in peak FEV_1 at Week 26 is based on the same statistical model used for the analysis of change from baseline in peak FEV_1 at all the other clinical visits, details on these secondary efficacy variables are also provided in this section.

The peak FEV_1 at a visit is calculated as the highest FEV_1 post dose value within 3 hours (5 measurements: 15min; 30min; 60min; 120min; 180min). Missing data will be handled as described in Section 4.13.

For Baseline peak FEV_1, please refer to the

Table 1: Baseline calculations.

Peak FEV_1 values at each visit will be summarised by treatment group using descriptive statistics. Changes from baseline at each visit will also be summarised by treatment group.

The above summary will be performed using the ITT and PP populations.

Change from baseline in peak FEV_1 will be analysed using a linear mixed model for repeated measures including treatment, visit, treatment by visit interaction, country as fixed effects, and baseline value and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed and the Kenward-Roger adjustment will be used for the degrees of freedom.

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

The adjusted means in each treatment group, the adjusted mean differences between treatments, their 95% CIs and associated p-values at each visit will be estimated by the model. Superiority of CHF 5993 pMDI HS over CHF 1535 pMDI HS will be demonstrated if the lower limit of the confidence interval for the adjusted mean difference between CHF 5993 pMDI HS and CHF 1535 pMDI HS at Week 26 is > 0.

The adjusted mean differences between CHF 5993 pMDI HS and CHF 1535 pMDI HS + Tiotropium and their 95% CIs will be estimated for descriptive purposes.

Similarly, the adjusted mean differences between CHF 1535 pMDI HS + Tiotropium and CHF 1535 pMDI HS and their 95% CIs will be also estimated for descriptive purposes.

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 mixed model will also be provided.

The above analysis will be performed using the ITT and PP populations.

In order to assess the potential impact of missing data on the results of this key secondary efficacy analysis, the same sensitivity analyses planned for pre-dose morning FEV_1 (see section 4.7.1.1) will be performed, with the following difference: the post-bronchodilator FEV_1 value at Visit 1, the pre-dose FEV_1 value at Visit 2 and the peak FEV_1 values from Visit 2 to Visit 7 will be considered in the imputation models (preliminary step and imputation under the MAR and CR assumptions) instead of pre-bronchodilator FEV_1 value at Visit 1 and pre-dose FEV_1 values from Visit 2 to Visit 7.

At each visit, the analysis will be based on the same ANCOVA model above described for the sensitivity analyses on pre-dose FEV_1. Estimates from the models will be then combined using Rubin's rule.

The analysis of Peak FEV1 based on the linear mixed model for repeated measures will be also presented on the ITT population by defined stratification factors described in section 4.1.5.

The adjusted mean differences between treatments at Week 26 (Visit 5) and at Week 52 (Visit 7) and their 95% CIs estimated on the ITT and PP populations, and in the sensitivity and stratified analyses, will be graphically summarised in a forest plot for each comparison between treatments (this means a total of 6 forest plots, one for each visit and treatment comparison).

4.7.2.2 Change from baseline in the average morning PEF over 26 weeks

Since the analysis of change from baseline in the average morning PEF over 26 weeks is based on the same statistical model used for the analysis of change from baseline in the average morning PEF over 52 weeks and in each-inter visit period, details on these secondary efficacy variables are also provided in this section.

For each day, the derived morning "Best PEF" for the statistical analysis will be calculated as the highest morning PEF value from all PEF measurements recorded pre-dose and with quality = "GOOD". The derived morning "Best PEF" for the statistical analysis will be calculated only for morning sessions recorded pre-dose and with at least two PEF measurements with quality = "GOOD".

Definitions of the periods to be calculated are reported in the below table:

Period	Definition
Baseline average morning PEF	Defined in the Table 1: Baseline calculations
Average morning PEF for each inter-visit period	The mean of all derived morning "Best PEF" values from the morning session of the day after Visit i to the morning session of the day of Visit i+1 (or the min(date of completion/discontinuation, date of visit 7 or date of early termination visit) for last inter-visit period) (with 'i' varying from 2 to 6). For the period Visit 2 – Visit 3, the day of start of randomised treatment period will be considered as reference point instead of day of Visit 2.

	The Average morning PEF will be calculated if at least 7 derived morning "Best PEF" values are available during the inter-visit period.
Average morning PEF over 26 weeks	The mean of all derived morning "Best PEF" values from the morning session of the day after the day of start of randomised treatment period to the morning session of day of Visit 5 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 5 (i.e., Visit 5 not performed)). The Average morning PEF will be calculated if at least 7 derived morning "Best PEF" values are available over the 26 weeks period.
Average morning PEF over 52 weeks	The mean of all derived morning "Best PEF" values from the morning session of the day after the day of start of randomised treatment period to the morning session of day of Visit 7 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 7 (i.e., Visit 7 not performed)). The Average morning PEF will be calculated if at least 7 derived morning "Best PEF" values are available over the 52 weeks period.
Mean change from baseline day by day by treatment group	The mean of the change from baseline of the derived morning "Best PEF" of all patients included in each study day (considering ITT population). To be calculated separately for each treatment. Study day will be calculated as: (date of the day – date of start of randomised treatment period +1).

Average morning PEF values at baseline, at each inter-visit period, over 26 weeks and over 52 weeks will be summarised by treatment group using descriptive statistics. Changes from baseline at each inter-visit period, over 26 weeks and over 52 weeks will also be summarised by treatment group.
Change from baseline in the average morning PEF will be analyzed using a linear mixed model for repeated measures including treatment, inter-visit period, treatment by inter-visit period interaction, country as fixed effects, and baseline value and baseline by period interaction as covariates. An unstructured covariance matrix will be assumed and the Kenward-Roger adjustment will be used for the degrees of freedom.
The number of patients considered in the model will be provided by treatment group. P-values of the effects will also be presented.
The adjusted means in each treatment group, the adjusted mean differences between treatments, their 95% CIs and associated p-values at each inter-visit period, over 26 weeks and over 52 weeks will be estimated by the model. In the evaluation over 26 weeks and over 52 weeks, a weight proportional to its expected duration will be assigned to each inter-visit period.
Superiority of CHF 5993 pMDI HS over CHF 1535 pMDI HS will be demonstrated if the lower limit of the confidence interval for the adjusted mean difference between CHF 5993 pMDI HS and CHF 1535 pMDI HS over 26 weeks is > 0.

The adjusted mean differences between CHF 5993 pMDI HS and CHF 1535 pMDI HS + Tiotropium and their 95% CIs will be estimated for descriptive purposes.

Similarly, the adjusted mean differences between CHF 1535 pMDI HS + Tiotropium and CHF 1535 pMDI HS and their 95% CIs will be also estimated for descriptive purposes.

A figure with adjusted mean change from baseline at each inter-visit period by treatment group derived from the linear mixed model will also be provided.
An additional figure describing the mean change from baseline of the derived morning "Best PEF" day by day for each treatment group will also be presented.

The above summary and statistical model will be performed on ITT and PP populations.

In order to assess the potential impact of missing data on the results of this key secondary efficacy analysis, the following sensitivity analyses based on multiple imputation (MI) will be performed on all randomised patients. In a preliminary step, imputation based on the missing at random (MAR) assumption will performed using the joint modelling approach in order to obtain monotone missing data patterns. The imputation will be performed considering the following variables: treatment, country, sex, height, weight, pre-bronchodilator FEV_1 value at Visit 1, baseline average morning PEF, average morning PEF for each inter-visit period (V2-V3, V3-V4, V4-V5, V5-V6, V6-V7). Then, a regression-based imputation will be performed according to the following strategies

- missing at random: imputation based on the MAR assumption in all treatment groups. The imputation model will correspond to the one used in the preliminary step. This analysis is based on the same assumption behind the MMRM used for the analysis of morning PEF, however it will allow the inclusion in the analysis of all randomised patients (this is not always possible with the MMRM);
- copy reference: imputation based on the data distribution of the CHF 5993 pMDI HS group in all treatment groups. The imputation model will correspond to the one used in the preliminary step, except for the exclusion of the treatment effect. This analysis mimics the case where discontinued patients in the CHF 1535 pMDI HS and CHF 1535 pMDI HS + Tiotropium arms are switched to the treatment with CHF 5993 pMDI HS (expected to be more effective than CHF 1535 pMDI HS and comparable to CHF 1535 pMDI HS + Tiotropium);
- baseline observation carried forward (BOCF) – like: imputation based on the distribution of baseline value in all treatment groups. The imputation model will include the following variables: country, sex, height, weight, pre-bronchodilator FEV_1 value at Visit 1, baseline value.

One thousand imputations will be performed and at each inter-visit period the analysis will be based on an ANCOVA model including the following variables: treatment, country as fixed effects, and baseline average morning PEF as covariate. Also the average values over 26 weeks and over 52 weeks will be analysed using the same ANCOVA model. Average over 26 weeks (and over 52 weeks) will be calculated considering the mean of the inter-visit period values (after imputation) weighted for the length of each inter-visit period, i.e., average 26 weeks = [(V2-V3 value)*4 + (V3-V4 value)*8 + (V4-V5 value)*14] / 26. A similar approach will be considered for average over 52 weeks.
Estimates from the models will be then combined using Rubin's rule.

The analysis of average morning PEF based on the linear mixed model for repeated measures will be also presented on the ITT population by defined stratification factors described in section 4.1.5.
The adjusted mean differences between treatments over 26 weeks and over 52 weeks and their 95% CIs estimated on the ITT and PP populations, and in the sensitivity and stratified

analyses, will be graphically summarised in a forest plot for each comparison between treatments (this means a total of 4 forest plots, one for each period and treatment comparison).

4.7.2.3 Severe asthma Exacerbation Rate over 52 Weeks of Treatment in the CCD-05993AB1-03 and CCD-05993AB2-02 pooled analysis

The pooled analysis of studies the CCD-05993AB1-03 and CCD-05993AB2-02 will be based on the following treatment groups (see also section 4.1.2):

- CHF 5993 pMDI + CHF 5993 pMDI HS, obtained by pooling the data from the CHF 5993 pMDI arm in study CCD-05993AB1-03 and the CHF 5993 pMDI HS arm in study CCD-05993AB2-02;
- CHF 1535 pMDI + CHF 1535 pMDI HS, obtained by pooling the data from the CHF 1535 pMDI arm in study CCD-05993AB1-03 and the CHF 1535 pMDI HS arm in study CCD-05993AB2-02.

Data from the CHF 1535 pMDI HS + Tiotropium group in study CCD-05993AB2-02 will not be included in the pooled analysis.

The number and the percentage of patients with moderate/severe asthma exacerbations, the number of moderate/severe asthma exacerbations and the total follow-up time in years will be summarised by treatment group (see section 4.7.1.2 for further details on the definition of moderate/severe asthma exacerbations and of the follow-up period).

The number of severe asthma exacerbations during the treatment period will be analysed using the same negative binomial model defined in section 4.7.1.2 for assessing the moderate and severe asthma exacerbation rate at the study-level. The adjusted asthma exacerbation rates in each treatment group and the adjusted rate ratio with its 95% Wald CI and p-value will be estimated by the model. Superiority of CHF 5993 pMDI + CHF 5993 pMDI HS over CHF 1535 pMDI + CHF 1535 pMDI HS will be demonstrated if the upper limit of the confidence interval for the adjusted rate ratio between CHF 5993 pMDI + CHF 5993 pMDI HS and CHF 1535 pMDI + CHF 1535 pMDI HS is < 1.

The results from the statistical model will be summarised as described in section 4.7.1.2.

The above summary/analysis will be performed using the ITT and PP populations.

The same stratified and sensitivity analyses planned described in section 4.7.1.2 will be performed.

4.7.3 Other Secondary Efficacy Variables

The other secondary efficacy variables are:

- Change from baseline in peak FEV_1 (within 3 hours post-dosing) at all clinical visits
- Change from baseline in pre-dose FEV_1 at all clinical visits
- FEV_1 response (change from baseline in pre-dose $FEV_1 \geq 100$ ml) at Week 26 and Week 52
- Change from baseline in FEV_1 $AUC_{0\text{-}3h}$ normalised by time at all clinical visits

- Change from baseline in the ACQ-7 score at all clinical visits
- ACQ-7 response (change from baseline in ACQ-7 score ≤ -0.5) at Week 26 and Week 52
- Change from baseline in morning and evening PEF in each inter-visit period, over the 26-week treatment period (evening PEF) and over the 52-week treatment period
- Time to first moderate or severe asthma exacerbation
- Time to first severe asthma exacerbation in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02
- Moderate asthma exacerbation rate over the 52-week treatment period in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02
- Time to first moderate asthma exacerbation in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02
- Moderate and severe asthma exacerbation rate over the 52-week treatment period in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02
- Time to first moderate or severe asthma exacerbation in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02
- Moderate asthma exacerbation rate over the 52-week treatment period
- Time to first moderate asthma exacerbation
- Change from baseline in the average use of rescue medication (number of puffs/day) in each inter-visit period, over the 26-week treatment period and over the 52-week treatment period
- Change from baseline in the percentage of rescue medication-free days in each inter-visit period, over the 26-week treatment period and over the 52-week treatment period
- Change from baseline in the average daily asthma symptoms scores in each inter-visit period, over the 26-week treatment period and over the 52-week treatment period
- Change from baseline in the percentage of asthma symptom free-days in each inter-visit period, over the 26-week treatment period and over the 52-week treatment period
- Change from baseline in the percentage of asthma control days in each inter-visit period, over the 26-week treatment period and over the 52-week treatment period

4.7.3.1 Change from baseline in peak FEV_1 at all clinical visits

Since the analysis of a key secondary efficacy variable (change from baseline in peak FEV_1 at Week 26, Visit 5) is based on the same descriptive analysis and statistical model used for the analysis of change from baseline in peak FEV_1 at Visits 2, 3, 4, 6 and 7, details on the analysis are provided in section 4.7.2.1.

4.7.3.2 Change from baseline in pre-dose FEV_1 at all clinical visits

Since the analysis of a co-primary efficacy variable (change from baseline in pre-dose FEV_1 at Week 26, Visit 5) is based on the same descriptive analysis and statistical model used for the analysis of change from baseline in pre-dose FEV_1 at Visits 3, 4, 6 and 7, details on the analysis are provided in section 4.7.1.1.

4.7.3.3 FEV_1 response at Week 26 and Week 52

FEV_1 response is defined as a change from baseline in pre-dose $FEV_1 \geq 100$ ml. If the change from baseline is greater than or equal to 100 ml the patient is classified as responder, otherwise if the change from baseline is lower than 100 ml the patient is classified as non-responder. Patients with missing change from baseline in pre-dose FEV_1 at the relevant time points will also be classified as non-responders (whatever the reason of the missing change from baseline value, patient withdrawn and no data are reallocated at the visit/time point, patient is present at the Visit but does not have a baseline value or does not have any value available at the visit/time point).

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 Visits 5 and 7 (Weeks 26 and 52) will be presented by treatment group.

FEV_1 response at Week 26 and Week 52 will be compared between treatment groups using a logistic model including treatment and country as factors and baseline pre-dose 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 HS vs. CHF 1535 pMDI HS with its 95% Wald CI and corresponding p-value will be estimated by the model.

The odds ratio for the treatment effect CHF 5993 pMDI HS vs. CHF 1535 pMDI HS + Tiotropium with its 95% Wald CI and corresponding p-value will be estimated for descriptive purposes.

Similarly, the odds ratio for the treatment effect CHF 1535 pMDI HS + Tiotropium vs. CHF 1535 pMDI HS with its 95% Wald CI and corresponding p-value will be also estimated for descriptive purposes.

The above summary/analysis will be performed using the ITT population.

4.7.3.4 Change from baseline in FEV_1 $AUC_{0\text{-}3h}$ normalised by time at all clinical visits

The FEV_1 $AUC_{0\text{-}3h}$ will be calculated at each visit by the sum of each AUC calculated by timepoint intervals (predose-15; 15-30; 30-60; 60-120; 120-180 min post-dose) using the linear trapezoidal method:

$$AUC_{0\text{-}3h} = \sum_{i=15min}^{180\,min} \frac{(t_i - t_{i\text{-}1})(FEV1_i + FEV1_{i\text{-}1})}{2}$$

with i = 0, 1, …, 5 referring to the measurements performed at pre-dose and 15 min, 30 min, 60 min, 120 min, 180 min post-dose, respectively.
In the above formula, t_i represents the actual time from dosing (first inhalation of study medication) in minutes (t_0 = 0) and $FEV1_i$ represents the value of the parameter at the timepoint *i* (pre-dose FEV_1 as defined in section 4.7.1.1 will be considered).
The FEV_1 $AUC_{0\text{-}3h}$ normalised by time is then obtained by dividing the FEV_1 $AUC_{0\text{-}3h}$ value by the actual duration (in minutes) of the assessments (corresponding to t_5).

Missing data will be dealt with as described in Section 4.13. The FEV_1 $AUC_{0\text{-}3h}$ will be calculated after the replacement of missing values.

For the baseline to be considered as covariate in the model, please refer to the

Table 1: Baseline calculations.

FEV_1 $AUC_{0\text{-}3h}$ normalised by time at each visit (visits 2, 3, 4, 5, 6, 7) will be summarised by treatment group using descriptive statistics. Changes from baseline at each visit will also be summarised by treatment group.

Change from baseline in FEV_1 $AUC_{0\text{-}3h}$ will be analysed using a linear mixed model for repeated measures including treatment, visit (visits 2, 3, 4, 5, 6, 7), treatment by visit interaction, country as fixed effects, and baseline value and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed and the Kenward-Roger adjustment will be used for the degrees of freedom.
The number of patients considered in the model will be provided by treatment group. P-values of the effects will also be presented.

The adjusted means in each treatment group, the adjusted mean differences between CHF 5993 pMDI HS and CHF 1535 pMDI HS, their 95% CIs and associated p-values at each visit will be estimated by the model. The adjusted mean differences between CHF 5993 pMDI HS and CHF 1535 pMDI HS + Tiotropium and their 95% CIs and associated p-values at each visit will be estimated for descriptive purposes. Similarly, the adjusted mean differences between CHF 1535 pMDI HS + Tiotropium and CHF 1535 pMDI HS and their 95% CIs and associated p-values at each visit will be also estimated for descriptive purposes.

A figure with adjusted mean at each visit by treatment group derived from the linear mixed model will also be provided.
The above summary/analysis will be performed using the ITT population.

4.7.3.5 Change from baseline in the ACQ-7 score at all clinical visits

ACQ-7 total score will be summarised at each visit by treatment group using descriptive statistics. Changes from baseline will also be summarised at each post-baseline visit by treatment group.

Change from baseline in the ACQ-7 score at all clinical visits will be analysed using the same models as for the primary efficacy analysis on pre-dose FEV_1 (see section 4.7.1.1), but including baseline ACQ-7 score instead of baseline FEV_1.

Missing data will be dealt with as described in Section 4.13.

For Baseline ACQ-7, please refer to the

Table 1: Baseline **calculations**.

A figure with adjusted mean change from baseline at each visit by treatment group derived from the linear mixed model will also be provided.

The above summaries/analyses will be performed using the ITT population.

4.7.3.6 ACQ-7 response at Week 26 and Week 52

ACQ-7 response is defined as a change from baseline in ACQ-7 score ≤ - 0.5. If the change from baseline is lower than or equal to - 0.5 the patient is classified as responder, otherwise if the change from baseline is greater than - 0.5 the patient is classified as non-responder. Patients with missing change from baseline in ACQ-7 score at the relevant time points will also be classified as non-responders (whatever the reason of the missing change from baseline value, patient withdrawn and no data are reallocated at the visit/time point, patient is present at the Visit but does not have a baseline value or does not have any value available at the visit/time point).

The number and percentage of ACQ-7 responders/non-responders (distinguishing also the two categories of non-responders: with a change from baseline actually ≤ - 0.5 or with missing data) at Visits 5 and 7 (Weeks 26 and 52) will be presented by treatment group.

ACQ-7 response at Week 26 and Week 52 will be compared between treatment groups using a logistic model including treatment and country as factors and baseline ACQ-7 score as a covariate.

The number of patients and 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 HS vs. CHF 1535 pMDI HS with its 95% Wald CI and corresponding p-value will be estimated by the model.

The odds ratio for the treatment effect CHF 5993 pMDI HS vs. CHF 1535 pMDI HS + Tiotropium with its 95% Wald CI and corresponding p-value will be estimated for descriptive purposes.

Similarly, the odds ratio for the treatment effect CHF 1535 pMDI HS + Tiotropium vs. CHF 1535 pMDI HS with its 95% Wald CI and corresponding p-value will be also estimated for descriptive purposes.

The above summary/analysis will be performed using the ITT population.

4.7.3.7 Change from baseline in average morning PEF in each inter-visit period and over 52 weeks and in average evening PEF in each inter-visit period and over 26 and 52 weeks

Since the analysis of a key secondary efficacy variable (change from baseline in the average morning PEF over 26 weeks) is based on the same descriptive analysis and statistical model used for the analysis of change from baseline in average morning PEF over 52 weeks and in each-inter visit period, details on the analysis are provided in section 4.7.2.2.

The derived evening “Best PEF” for the statistical analysis will be calculated as the highest evening PEF value from all PEF measurements recorded pre-dose and with quality =

"GOOD". The derived evening "Best PEF" for the statistical analysis will be calculated only for evening sessions with at least two PEF measurements recorded pre-dose and with quality = "GOOD".

Definitions of the periods to be calculated are reported in the below table:

Period	Definition
Baseline average evening PEF	Defined in the Table 1: Baseline calculations
Average evening PEF for each inter-visit period	The mean of all derived evening "Best PEF" values from the evening session of the day of Visit i to the evening session of the day before Visit i+1 (or the min(date of completion/discontinuation, date of visit 7 or date of early termination visit) for last inter-visit period) (with 'i' varying from 2 to 6). For the period Visit 2 – Visit 3, the day of start of randomised treatment period will be considered as reference point instead of day of Visit 2. The Average evening PEF will be calculated if at least 7 derived evening "Best PEF" values are available during the inter-visit period.
Average evening PEF over 26 weeks	The mean of all derived evening "Best PEF" values from the evening session of the day of start of randomised treatment period to the evening session of day before Visit 5 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 5 (i.e., Visit 5 not performed)). The Average evening PEF will be calculated if at least 7 derived evening "Best PEF" values are available over the 26 weeks period.
Average evening PEF over 52 weeks	The mean of all derived evening "Best PEF" values from the evening session of the day of start of randomised treatment period to the evening session of day before Visit 7 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 7 (i.e., Visit 7 not performed)). The Average evening PEF will be calculated if at least 7 derived evening "Best PEF" values are available over the 52 weeks period.
Mean change from baseline day by day by treatment group	The mean of the change from baseline of the derived evening "Best PEF" value of all patients included in each study day (considering ITT population). To be calculated separately for each treatment. Study day will be calculated as: (date of the day – date of start of randomised treatment period +1).

The same summary/analysis planned for change from baseline in average morning PEF (with the exception of sensitivity and stratified analyses, see section 4.7.2.2) will be performed for change from baseline in average evening PEF using the ITT population.

4.7.3.8 Time to first moderate or severe asthma exacerbation

Regarding the asthma exacerbations to be considered in the analysis and the asthma exacerbations to be considered as a single episode, see section 4.7.1.2.

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

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

Patients without a moderate or severe asthma exacerbation or who are discontinued before having it will be considered as "censored" at min(date of completion/discontinuation, date of Visit 7 or study termination visit). For the analysis, the following formula will be applied:

- Censoring time (weeks) = (min(date of completion/discontinuation, date of Visit 7 or study termination visit) – date of start of randomised treatment period)/7

The number of moderate or severe asthma exacerbation-free patients at the beginning of the period, the cumulative number of patients with moderate or severe asthma exacerbation at the end of the period and the probability of having experienced a moderate or severe asthma at the end of the period with the associate 95% CIs will be presented by treatment group for the following study periods: [0-4) weeks, [4-12) weeks, [12-26) weeks, [26-40) weeks, [40-52) weeks, [52-EoT] weeks. The point estimates and the relative 95% CIs will be presented by treatment group for the 75th, 50th and 25th percentiles. A Kaplan-Meier plot will also be presented.

The time to first moderate or severe asthma exacerbation will be analysed using a Cox proportional hazards model including treatment, country and number of asthma exacerbations in the previous year (1 or >1) 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 HS vs. CHF 1535 pMDI HS will be presented as a hazard ratio with the associated 95% Wald CI and p-value.

The hazard ratio for the treatment effect CHF 5993 pMDI HS vs. CHF 1535 pMDI HS + Tiotropium with its 95% Wald CI and corresponding p-value will be estimated for descriptive purposes.

Similarly, the hazard ratio for the treatment effect CHF 1535 pMDI HS + Tiotropium vs. CHF 1535 pMDI HS with its 95% Wald CI and corresponding p-value will be also estimated for descriptive purposes.

The above summary/analysis will be performed using the ITT population.

4.7.3.9 Moderate asthma exacerbation rate over the 52-week treatment period

The number of moderate asthma exacerbations during the treatment period will be analysed on the ITT population using the same negative binomial model as for the moderate and severe asthma exacerbations (see section 4.7.1.2).

4.7.3.10 Time to first moderate asthma exacerbation

The same summary/analysis planned for time to first moderate or severe asthma exacerbation (see section 4.7.3.8) will be performed for time to first moderate asthma exacerbation.

4.7.3.11 Time to first severe asthma exacerbation in the CCD-05993AB1-03 and CCD-05993AB2-02 pooled analysis

For details on the treatment groups to be considered in the pooled analysis, see section 4.7.2.3.

The same summary/analysis planned for time to first moderate or severe asthma exacerbation at the study-level (see section 4.7.3.8) will be performed for time to first severe asthma exacerbation in the pooled analysis of CCD-05993AB1-03 and CCD-05993AB2-02 studies. Treatment groups CHF 5993 pMDI + CHF 5993 pMDI HS and CHF 1535 pMDI + CHF 1535 pMDI HS will be compared.

4.7.3.12 Moderate asthma exacerbation rate over the 52-week treatment period in the CCD-05993AB1-03 and CCD-05993AB2-02 pooled analysis

For details on the treatment groups to be considered in the pooled analysis, see section 4.7.2.3.

The pooled analysis of the of moderate asthma exacerbation rate during the treatment period in studies CCD-05993AB1-03 and CCD-05993AB2-02 will be performed on the ITT population using the same negative binomial model defined in section 4.7.1.2 for assessing the moderate and severe asthma exacerbation rate at the study-level. Treatment groups CHF 5993 pMDI + CHF 5993 pMDI HS and CHF 1535 pMDI + CHF 1535 pMDI HS will be compared.

4.7.3.13 Time to first moderate asthma exacerbation in the CCD-05993AB1-03 and CCD-05993AB2-02 pooled analysis

For details on the treatment groups to be considered in the pooled analysis, see section 4.7.2.3.

The same summary/analysis planned for time to first moderate or severe asthma exacerbation at the study-level (see section 4.7.3.8) will be performed for time to first moderate asthma exacerbation in the pooled analysis of CCD-05993AB1-03 and CCD-05993AB2-02 studies. Treatment groups CHF 5993 pMDI + CHF 5993 pMDI HS and CHF 1535 pMDI + CHF 1535 pMDI HS will be compared.

4.7.3.14 Moderate and severe asthma exacerbation rate over the 52-week treatment period in the CCD-05993AB1-03 and CCD-05993AB2-02 pooled analysis

For details on the treatment groups to be considered in the pooled analysis, see section 4.7.2.3.

The pooled analysis of the of moderate and severe asthma exacerbation rate during the treatment period in studies CCD-05993AB1-03 and CCD-05993AB2-02 will be performed on the ITT population using the same negative binomial model defined in section 4.7.1.2 for assessing the moderate and severe asthma exacerbation rate at the study-level. Treatment groups CHF 5993 pMDI + CHF 5993 pMDI HS and CHF 1535 pMDI + CHF 1535 pMDI HS will be compared.

4.7.3.15 Time to first moderate or severe asthma exacerbation in the CCD-05993AB1-03 and CCD-05993AB2-02 pooled analysis

For details on the treatment groups to be considered in the pooled analysis, see section 4.7.2.3.
The same summary/analysis planned for time to first moderate or severe asthma exacerbation at the study-level (see section 4.7.3.8) will be performed for time to first moderate or severe asthma exacerbation in the pooled analysis of CCD-05993AB1-03 and CCD-05993AB2-02 studies. Treatment groups CHF 5993 pMDI + CHF 5993 pMDI HS and CHF 1535 pMDI + CHF 1535 pMDI HS will be compared.

4.7.3.16 Change from baseline in the average use of rescue medication in each inter-visit period and over 26 and 52 weeks

A day will be constituted by the data recorded in the evening session of that day plus the data recorded in the morning session of the next day.
For each day, the "daily use of rescue medication" will be calculated as the sum of the number of puffs taken during the day (recorded in the PM session of the day - Q7 for treatment questionnaire)) and taken during the night (recorded in the AM session of the next day - Q9 for treatment questionnaire).
If one of the two sessions (evening or morning) associated with the day is missing, the daily use of rescue medication in that day will be calculated using the available session only.

Definitions of the periods to be calculated are reported in the below table:

Period	Definition
Baseline average use of rescue medication	Defined in the Table 1: Baseline calculations
Average use of rescue medication for each inter-visit period	The mean of the daily use of rescue medication of the data recorded from the evening session of the day of Visit i to the morning session of the day of Visit i+1 (or the min(date of completion/discontinuation, date of visit 7 or date of early termination visit) for last inter-visit period) (with 'i' varying from 2 to 6). For the period Visit 2 – Visit 3, the day of start of randomised treatment period will be considered as reference point instead of day of Visit 2. The Average use of rescue medication will be calculated if at least 7 daily use of rescue medication will be available on the data of the inter-visit period.
Average use of rescue medication over 26 weeks	The mean of the daily use of rescue medication of the data recorded from the evening session of the day of start of randomised treatment period to the morning session of the day of Visit 5 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 5 (i.e., Visit 5 not performed)). The Average use of rescue medication will be calculated if at least 7 daily use of rescue medication will be available on the data available over the 26 weeks period.
Average use of rescue medication	The mean of the daily use of rescue medication puffs of the data recorded from the evening session of the day of start of randomised

over 52 weeks	treatment period to the morning session of the day of Visit7 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 7 (i.e., Visit 5 not performed)). The Average use of rescue medication will be calculated if at least 7 daily use of rescue medication will be available on the data available over the 52 weeks period.
Mean change from baseline day by day by treatment group	The mean of the change from baseline in daily use of rescue medication of all patients included in each study day (considering ITT population). To be calculated separately for each treatment. Study day will be calculated as: (date of the day – date of start of randomised treatment period +1).

The same summary/analysis planned for change from baseline in average morning PEF (with the exception of sensitivity and stratified analyses, see section 4.7.2.2) will be performed for change from baseline in the average use of rescue medication using the ITT population.

4.7.3.17 Change from baseline in the percentage of rescue medication-free days in each inter-visit period and over 26 and 52 weeks

A day will be constituted by the data recorded in the evening session of that day plus the data recorded in the morning session of the next day.
A rescue medication-free day is a day with daily use of rescue medication = 0.

Definitions of the periods to be calculated are reported in the below table:

Period	Definition
Baseline of percentage of rescue medication-free days	Defined in the Table 1: Baseline calculations
Percentage of rescue medication-free days for each inter-visit period	100*(number of rescue medication-free days during the inter-visit period / number of days with available daily use of rescue medication during the inter-visit period) with number of rescue medication-free days during the inter-visit period and number of days with available daily use of rescue medication during the inter-visit period calculated on the data recorded from the evening session of the day of Visit i to the morning session of the day of Visit i+1 (or the min(date of completion/discontinuation, date of visit 7 or date of early termination visit) for last inter-visit period) (with 'i' varying from 2 to 6). For the period Visit 2 – Visit 3, the day of start of randomised treatment period will be considered as reference point instead of day of Visit 2. A minimum of 7 days with available daily use of rescue medication will be required in the inter-visit period to consider the percentage of rescue medication-free days as non-missing.
Percentage of rescue medication-free days over 26 weeks	100*(number of rescue medication-free days over 26 weeks / number of days with available daily use of rescue medication over 26 weeks) with number of rescue medication-free days over 26 weeks and number of days with available daily use of rescue medication over 26 weeks

	calculated on the data recorded from the evening session of the day of start of randomised treatment period to the morning session of the day of Visit 5 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 5 (i.e., Visit 5 not performed)) A minimum of 7 days with available daily use of rescue medication will be required over the 26 weeks period to consider the percentage of rescue medication-free days as non-missing.
Percentage of rescue medication-free days over 52 weeks	100*(number of rescue medication-free days over 52 weeks / number of days with available daily use of rescue medication over 52 weeks) with number of rescue medication-free days over 52 weeks and number of days with available daily use of rescue medication over 52 weeks calculated on the data recorded from the evening session of the day of start of randomised treatment period to the morning session of the day of Visit 7 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 7 (i.e., Visit 7 not performed)) A minimum of 7 days with available daily use of rescue medication will be required over the 52 weeks period to consider the percentage of rescue medication-free days as non-missing.

The same summary/analysis planned for change from baseline in average morning PEF (with the exception of sensitivity and stratified analyses, see section 4.7.2.2) will be performed for change from baseline in the percentage of rescue medication-free days using the ITT population.

4.7.3.18 Change from baseline in the average daily asthma symptoms scores in each inter-visit period and over 26 and 52 weeks

Asthma symptom scores will be recorded daily by the patient (each morning and evening) for cough, wheeze, chest tightness and breathlessness scores, and each morning only for the overall night-time asthma symptoms score, as follows:

IN THE MORNING (night-time asthma symptom score):

- 0 = No symptom
- 1 = Mild: symptoms not causing awakening
- 2 = Moderate: discomfort enough to cause awakening
- 3 = Severe: causing awakening for most of the night / do not allow to sleep at all

IN THE EVENING (day-time asthma symptom score):

- 0 = No symptom
- 1 = Mild: aware of symptoms which can be easily tolerated
- 2 = Moderate: discomfort enough to cause interference with daily activity
- 3 = Severe: incapacitating with inability to work / take part in usual activity

For cough, wheeze, chest tightness and breathlessness scores, a day will be constituted by the data recorded in the evening session of that day plus the data recorded in the morning session of the next day.

For each day of the treatment period:

- the "total daily asthma symptoms score" will be calculated as the mean of the 8 scores (i.e, 4 evening symptoms scores of the day (Q3-Q6 for treatment questionnaire) and 4 morning symptoms scores of the next day (Q4-Q7 for treatment questionnaire));
- for each symptoms, the "daily symptom score" will be calculated as the mean of the evening symptom score of the day and morning symptoms score of the next day.

If one of the two sessions (evening or morning) associated with the day is missing, the daily symptom score will be calculated on the available session only.

Definition of the periods to be calculated for "total daily asthma symptom score" and each single "daily asthma symptom score" are reported in the below table:

Period	Definition
Baseline average daily asthma symptoms score	Defined in the Table 1: Baseline **calculations**
Average daily asthma symptoms score for each inter-visit period	The mean of the daily asthma symptoms scores of the data recorded from the evening session of the day of Visit i to the morning session of the day of Visit i+1 (or the min(date of completion/discontinuation, date of visit 7 or date of early termination visit) for last inter-visit period) (with 'i' varying from 2 to 6). For the period Visit 2 – Visit 3, the day of start of randomised treatment period will be considered as reference point instead of day of Visit 2. The Average daily asthma symptoms score will be calculated if at least 7 daily asthma symptoms scores will be available on the data of the inter-visit period.
Average daily asthma symptoms score over 26 weeks	The mean of the daily asthma symptoms scores of the data recorded from the evening session of the day of start of randomised treatment period to the morning session of the day of Visit 5 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 5 (i.e., Visit 5 not performed)). The Average daily asthma symptoms score will be calculated if at least 7 daily asthma symptoms scores will be available on the data over the 26 weeks period.
Average daily asthma symptoms score over 52 weeks	The mean of the daily asthma symptoms scores of the data recorded from the evening session of the day of start of randomised treatment period to the morning session of the day of Visit 7 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 7 (i.e., Visit 7 not performed) for discontinued patients) The Average daily asthma symptoms scores will be calculated if at least 7 daily asthma symptoms score will be available on the data over the 52 weeks period.
Mean change from	The mean of the change from baseline in daily asthma symptoms scores

baseline day by day by treatment group	of all patients included in each study day (considering ITT population). To be calculated separately for each treatment. Study day will be calculated as: (date of the day – date of start of randomised treatment period +1).

For the "overall night-time asthma symptoms score", a day will be constituted by the data recorded in the morning session of the next day.

Definition of the periods to be calculated for overall night-time asthma symptoms score are reported in the below table:

Period	Definition
Baseline average overall night-time asthma symptoms score	Defined in the Table 1: Baseline **calculations**
Average overall night-time asthma symptoms score for each inter-visit period	The mean of the overall night-time asthma symptoms scores of the data recorded from the morning session of the day after Visit i to the morning session of the day of Visit i+1 (or the min(date of completion/discontinuation, date of visit 7 or date of early termination visit) for last inter-visit period) (with 'i' varying from 2 to 6). For the period Visit 2 – Visit 3, the day of start of randomised treatment period will be considered as reference point instead of day of Visit 2. The average overall night-time asthma symptoms score will be calculated if at least 7 overall night-time asthma symptoms scores will be available on the data of the inter-visit period.
Average overall night-time asthma symptoms score over 26 weeks	The mean of the overall night-time asthma symptoms scores of the data recorded from the morning session of the day after the date of start of randomised treatment period to the morning session of the day of Visit 5 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 5 (i.e., Visit 5 not performed)). The average overall night-time asthma symptoms score will be calculated if at least 7 overall night-time asthma symptoms scores will be available on the data over the 26 weeks period.
Average overall night-time asthma symptoms score over 52 weeks	The mean of the overall night-time asthma symptoms scores of the data recorded from the morning session of the day after the date of start of randomised treatment period to the morning session of the day of Visit 7 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 7 (i.e., Visit 7 not performed)). The average overall night-time asthma symptoms score will be calculated if at least 7 overall night-time asthma symptoms scores will be available on the data over the 52 weeks period.
Mean change from baseline day by day by treatment group	The mean of the change from baseline in overall night-time asthma symptoms scores of all patients included in each study day (considering ITT population). To be calculated separately for each treatment. Study day will be calculated as: (date of the day – date of start of randomised treatment period +1).

The same summary/analysis planned for change from baseline in average morning PEF (with the exception of sensitivity and stratified analyses, see section 4.7.2.2) will be performed for the following variables using the ITT population:

- change from baseline in the average total daily asthma symptoms score;
- change from baseline in the average cough, wheeze, chest tightness and breathlessness symptom scores;
- change from baseline in the average overall night-time asthma symptoms score.

4.7.3.19 Change from baseline in the percentage of asthma symptom-free days in each inter-visit period and over 26 and 52 weeks

A day will be constituted by the data recorded in the evening session of that day plus the data recorded in the morning session of the next day.
An asthma symptom-free day is a day with total daily asthma symptom score = 0.

Definitions of the periods to be calculated are reported in the below table:

Period	Definition
Baseline of percentage of asthma symptom-free days	Defined in the Table 1: Baseline calculations
Percentage of asthma symptom-free days for each inter-visit period	100*(number of asthma symptom-free days during the inter-visit period / number of days with available total daily asthma symptom score during the inter-visit period) with number of asthma symptom-free days during the inter-visit period and number of days with available total daily asthma symptom score during the inter-visit period calculated on the data recorded from the evening session of the day of Visit i to the morning session of the day of Visit i+1 (or the min(date of completion/discontinuation, date of visit 7 or date of early termination visit) for last inter-visit period) (with 'i' varying from 2 to 6). For the period Visit 2 – Visit 3, the day of start of randomised treatment period will be considered as reference point instead of day of Visit 2. A minimum of 7 days with available total daily asthma symptom score will be required in the inter-visit period to consider the percentage of asthma symptom-free days as non-missing.
Percentage of asthma symptom-free days over 26 weeks	100*(number of asthma symptom-free days over 26 weeks / number of days with available total daily asthma symptom score over 26 weeks) with number of asthma symptom-free days over 26 weeks and number of days with available total daily asthma symptom score over 26 weeks calculated on the data recorded from the evening session of the day of start of randomised treatment period to the morning session of the day of Visit 5 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 5 (i.e., Visit 5 not performed))

	A minimum of 7 days with available total daily asthma symptom score will be required over the 26 weeks period to consider the percentage of asthma symptom-free days as non-missing.
Percentage of asthma symptom-free days over 52 weeks	100*(number of asthma symptom-free days over 52 weeks / number of days with available total daily asthma symptom score over 52 weeks) with number of asthma symptom-free days over 52 weeks and number of days with available total daily asthma symptom score over 52 weeks calculated on the data recorded from the evening session of the day of start of randomised treatment period to the morning session of the day of Visit 7 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 7 (i.e., Visit 7 not performed)) A minimum of 7 days with available total daily asthma symptom score will be required over the 52 weeks period to consider the percentage of asthma symptom-free days as non-missing.

The same summary/analysis planned for change from baseline in average morning PEF (with the exception of sensitivity and stratified analyses, see section 4.7.2.2) will be performed for change from baseline in the percentage of asthma symptom-free days using the ITT population.

4.7.3.20 Change from baseline in the percentage of asthma control days in each inter-visit period and over 26 and 52 weeks

A day will be constituted by the data recorded in the evening session of that day plus the data recorded in the morning session of the next day.
An asthma control day is a day with total daily asthma symptom score = 0 and daily use of rescue medication = 0.

Definitions of the periods to be calculated are reported in the below table:

Period	Definition
Baseline of percentage of asthma control days	Defined in the Table 1: Baseline calculations
Percentage of asthma control days for each inter-visit period	100*(number of asthma control days during the inter-visit period / number of days with available both total daily asthma symptom score and daily use of rescue medication during the inter-visit period) With number of asthma control days during the inter-visit period and number of days with available both total daily asthma symptom score and daily use of rescue medication during the inter-visit period calculated on the data recorded from the evening session of the day of Visit i to the morning session of the day of Visit i+1 (or the min(date of completion/discontinuation, date of visit 7 or date of early termination visit) for last inter-visit period) (with 'i' varying from 2 to 6).

	For the period Visit 2 – Visit 3, the day of start of randomised treatment period will be considered as reference point instead of day of Visit 2. A minimum of 7 days with available both total daily asthma symptom score and daily use of rescue medication will be required in the inter-visit period to consider the percentage of asthma control days as non-missing.
Percentage of asthma control days over 26 weeks	100*(number of asthma control days over 26 weeks / number of days with available both total daily asthma symptom score and daily use of rescue medication over 26 weeks) with number of asthma control days over 26 weeks and number of days with available both total daily asthma symptom score and daily use of rescue medication over 26 weeks calculated on the data recorded from the evening session of the day of start of randomised treatment period to the morning session of the day of Visit 5 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 5 (i.e., Visit 5 not performed)) A minimum of 7 days with available both total daily asthma symptom score and daily use of rescue medication will be required over the 26 weeks period to consider the percentage of asthma control days as non-missing.
Percentage of asthma control days over 52 weeks	100*(number of asthma control days over 52 weeks / number of days with available both total daily asthma symptom score and daily use of rescue medication over 52 weeks) with number of asthma control days over 52 weeks and number of days with available both total daily asthma symptom score and daily use of rescue medication over 52 weeks calculated on the data recorded from the evening session of the day of start of randomised treatment period to the morning session of the day of Visit 7 (or the min(date of completion/discontinuation, date of early termination visit) for discontinued patients before Visit 7 (i.e., Visit 7 not performed)) A minimum of 7 days with available total both daily asthma symptom score and daily use of rescue medication will be required over the 52 weeks period to consider the percentage of asthma control days as non-missing.

The same summary/analysis planned for change from baseline in average morning PEF (with the exception of sensitivity and stratified analyses, see section 4.7.2.2) will be performed for change from baseline in the percentage of asthma control days using the ITT population.

4.7.4 Exploratory Efficacy Variables

The exploratory efficacy variables are:

- Pre-dose FVC, IC and VC at all clinical visits

4.7.4.1 Pre-dose FVC, IC and VC at all Clinical Visits

Pre-dose FVC values will be summarised at each visit by treatment group using descriptive statistics. Changes from baseline will also be summarised at each post-baseline visit by treatment group. In order to provide a comprehensive description of the results on this parameter, the post-dose FVC values and their changes from baseline will be included in this summary table as well.

The above summary/analysis will be performed using the ITT population.

The same descriptive analysis will be performed for pre-dose IC and VC parameters.

For Baseline pre-dose FVC, IC and VC, please refer to the

Table 1: Baseline calculations.

4.8 Health Economic Variables

The health economic variables are:

- EQ-5D-3L VAS score and EQ-5D-3L index at all clinical visits
- Number of hospital admissions due to asthma
- Number of days in hospital due to asthma
- Number of emergency room visits due to asthma
- Number of unscheduled contacts with health care providers due to asthma:
  - Family practitioner
  - Specialist outpatient setting
  - Specialist hospital outpatient setting
- Unplanned diagnostic tests or instrumental tests due to asthma
- Concomitant medications
- Lost productivity (sick leave days from work, retirement) due to asthma.

4.8.1.1 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: [redacted]

The algorithm for the calculation of the EQ-5D-3L index is provided in the Appendix III: EQ-5D-3L algorithm.

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).

The above summary will be performed using the ITT population.

4.8.1.2 Other Health Economic Data

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

- Number of hospital admissions due to asthma;
- Number of hospital days due to asthma;
- Number of emergency room visits due to asthma;
- Number of unscheduled contacts with health care providers due to asthma:
  - family practitioner;
  - specialist outpatient setting;
  - specialist hospital outpatients setting;
- Unplanned diagnostic tests or instrumental tests due to asthma
- Lost productivity (sick leave days from work) due to asthma

A descriptive summary of the total number of events/days/tests will be presented by treatment group. Of note, the descriptive summary based on totals does not take into account the differences in the follow-up duration of the patients and the potential impact of missing data.

The patient professional status at Visit 2 and the retirements due to sickness occurred during the study will be summarised. Retirements due to 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.

The above summary will be performed using the ITT population.

4.9 Safety Analysis

All safety variables will be summarised using the safety population.

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 treatment will be also summarised.

4.9.1 Exposure to Randomised Study Treatment

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.

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

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

- [0-4)
- [4-8)
- [8-12)
- [12-16)
- [16-20)
- [20-24)
- [24-28)
- [28-32)
- [32-36)
- [36-40)
- [40-44)
- [44-48)
- [48-52)
- ≥52.

4.9.2 Adverse Events

Asthma exacerbations reported in the Asthma Exacerbation form of the eCRF will be also included in the analysis of AEs (tables and listings). When asthma exacerbations are analysed as AEs no aggregation of asthma exacerbations close in time will be performed.

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 it starts on or after the first randomised study medication intake up to min(date of completion/discontinuation, date of Visit 7 or study termination visit) (date of first randomised study medication intake ≤ AE onset date ≤ min(date of completion/discontinuation, date of Visit 7 or study termination visit)).

An AE will be classified as a post-study AE if it starts after min(date of completion/discontinuation, date of Visit 7 or study termination visit) (AE onset date > min(date of completion/discontinuation, date of Visit 7 or study termination visit)).

A serious AE is an AE judged as serious.

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

A serious ADR is a SAE judged as related to the study medication.

A severe AE is an AE with severe intensity.

An AE leading to discontinuation is an AE with action taken with study drug equal to “Permanently discontinued”.

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

MACEs will be identified before the database lock by an adjudication committee involving external expert advisors. An evaluation of the following AEs will be performed:

- **Acute MI** (acute coronary syndrome, non-fatal myocardial infarction);
- **Stroke** (fatal or non-fatal stroke);
- **Cardiovascular death** (cardiac arrest, sudden death);
- **Arrhythmias**: New sustained supraventricular arrhythmias (including atrial fibrillation and atrial flutter) and sustained ventricular tachyarrhythmias. Sustained arrhythmias are defined as those with duration ≥ 30 seconds or requiring earlier termination due to hemodynamic intolerance;
- **Heart Failure** (change in the status: NYHA classification).

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 randomised 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 has 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 – min(date of completion/discontinuation, date of Visit 7 or study termination visit) (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 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 and AEs leading to death will be summarised by treatment group.

AEs will be coded using the MedDRA dictionary (version 18.1). 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, AEs leading to death and MACEs leading to death, non-serious AEs.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, sorted by decreasing overall frequency.

The number and percentage of patients with at least one treatment emergent MACE and the number of treatment emergent MACEs will be presented by treatment group using the categorisation defined. The same analysis will be performed for MACEs leading to death only.

MACEs 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:

- Follow-up time (years) = [min(date of completion/discontinuation, date of Visit 7 or study termination visit) - date of first randomised study medication intake + 1] / 365.25.

The rate of MACE (any MACE and relevant categories of MACEs) per 1’000 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 1’000).

All the analyses of AEs and MACEs above described will be performed also by stratified factors described in section 4.1.5.

MACEs stratified analyses will be carried out only if more than 10 MACEs will be reported by the adjudication committee.

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 45 min post-dose at each visit will also be summarised. 95% CIs for the mean changes from baseline/pre-dose will also be presented.

For Baseline SBP and DBP, please refer to the

Table 1: Baseline **calculations**.

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 45 min post-dose at Visits 2 to 7.

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 randomised study medication intake, and the changes from pre-dose to 45 min post-dose at Visits 3 to 7 will be summarised by treatment group. 95% CIs for the mean absolute values and 90% CIs for the mean changes from baseline will also be presented.

For Baseline 12-lead ECG, please refer to the

Table 1: Baseline **calculations**.

Change from baseline (Visit 2 pre-dose) in pre-dose 12-lead ECG parameters (HR, QTcF, PR and QRS) will be analysed using a similar model as for the change from baseline in pre-dose FEV_1 (see section 4.7.1.1). The adjusted means in each treatment group and the adjusted mean differences between treatments at each visit will be estimated by the model with their 90% CIs. The same analysis will be performed for change from baseline (Visit 2 pre-dose) in post-dose 12-lead ECG parameters.

At each visit (from Visit 3 onwards), the change from pre-dose to post-dose in the 12-lead ECG parameters (HR, QTcF, PR and QRS) will be analysed using an ANCOVA model including treatment, country as fixed effects, and the pre-dose value at the visit as a covariate. The adjusted means in each treatment group and the adjusted mean differences between treatments will be estimated by the model with their 90% CIs.

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 each time point after the first randomised study medication intake and at any time point after the first randomised study medication intake will be presented by treatment group.

Patients with pacemaker or atrial fibrillation as concomitant disease and ECGs with PR=0 will be excluded from the analysis of 12-lead ECG parameters.

Summaries/analyses of HR and QTcF parameters will be also performed stratifying by use of spacer (as described in section 4.1.5).

4.9.5 24-hour Holter ECG

24-hour Holter monitoring will be performed in a subset of patients at Visit 1, 2, 4, 5 and 7.

24-hour average HR at Visits 2, 4, 5 and 7 and changes from baseline (Visit 2) in 24-hour average HR at Visits 4, 5 and 7 will be summarised by treatment group using the Holter Subset. 95% CIs for the mean absolute values and the changes from baseline will also be presented.

In case of 24-hour Holter ECG at Visit 2 including an end date time after the study medication intake date time:

- Baseline for 24-hour Holter ECG HR average, HR minimum and HR maximum will be re-calculated using all hourly session having an end time before the study medication intake date time.

For the HR average, the single HR average of each hourly session will be weighted by the real duration of the hour session with available assessment in minute.

- Baseline for the other parameters (not HR average, HR minimum or HR maximum) will be considered as missing

Change from baseline in 24-hour average HR will be analysed using a similar model as for change from baseline in pre-dose FEV_1 (see Section 4.7.1.1) using the Holter Subset.

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.

The following variables obtained from the 24 h Holter evaluation at Visits 4, 5 and 7 will be summarised by treatment group using descriptive statistics in the Holter subset:

1. Minimum HR (bpm);
2. Maximum HR (bpm);
3. Longest Tachycardia Duration (min);
4. Longest Tachycardia Maximum HR (bpm);
5. Fastest Tachycardia Duration (min);
6. Fastest Tachycardia Maximum HR (bpm);
7. Longest Bradycardia Duration (min);
8. Longest Bradycardia Minimum HR (bpm);
9. Slowest Bradycardia Duration (min);
10. Slowest Bradycardia Minimum HR (bpm);
11. Time in Atrial Fibrillation Percentage;
12. Atrial Fibrillation Peak Average Rate (bpm);
13. Supraventricular Total;
14. Ventricular Total;
15. RR > 2 sec (yes/no: yes if number of RR > 2 sec > 0, no if number of RR > 2 sec = 0).

The analyses above described, of 24-hour average HR (except for the analysis based on the statistical model) and of the Holter variables from 1 to 10, will be performed also stratifying by use of spacer (as described in section 4.1.5).

The following variables obtained from the 24 h Holter evaluation will be only presented in the listings:

- Number of Tachycardia incidents;
- Superventricular Ectopy Couplets;
- Superventricular Ectopy Runs;
- Superventricular Ectopy Singles;
- Ventricular Ectopy Couplets;
- Ventricular Ectopy Runs;

Ventricular Ectopy Singles.

4.9.6 Laboratory Findings

The following laboratory parameters will be recorded at Visit 1 (Screening), Visit 5 (Week 26) and Visit 7 (Week 52):

Haematology:

Red blood cell (RBC) count, white blood cell (WBC) count and differential (basophils, eosinophils, lymphocytes, monocytes and neutrophils), total haemoglobin (Hb), haematocrit (Hct), 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, albumin, alkaline phosphatase, cholesterol, triglycerides, uric acid, total proteins, sodium (Na), potassium (K), calcium (Ca), and chloride (Cl) electrolytes.

In addition, serum Beta-Human Chorionic Gonadotropin (β-HCG) will be performed (only for females of childbearing potential) at Visit 1 and Visit 7 and a urine pregnancy test will also be performed at Visits 1 to 6.

Shift tables from screening to Week 26 and Week 52, with regard to normal range (low, normal and high), will be presented by treatment group for each of the laboratory parameters.

Pregnancy test results will be only listed.

4.10 Other Data

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

4.11 Adjustment for Covariates

All ANCOVA models, repeated measures models and logistic models will include the baseline (please refer to the

Table 1: Baseline **calculations**) value of the variable as covariate and country as fixed effect. Repeated measures models will also include visit/inter-visit period, the treatment by visit/inter-visit period interaction and the baseline by visit/inter-visit period interaction. The negative binomial model and the Cox proportional hazards model will include country and

number of asthma exacerbations in the previous year (1 or >1), as fixed effects. The negative binomial model will also include the log-time on study in years as an offset.

In the analyses stratified by one of the factors included in the statistical model used for the non-stratified analysis, the factor will be removed from the model (e.g., in the analysis stratified by the number of asthma exacerbations in the previous year (1 or >1), the number of asthma exacerbations in the previous year 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;
- effects of quantitative covariates set equal to their mean values in the group of patients analysed.

4.11.1 Centre Effects

In order to define groups with a sufficient number of patients (taking also into account the stratified analyses), initially countries will be combined into the following regions:

- Western Europe: Germany, Italy, Spain, United Kingdom, Portugal;
- Eastern Europe 1: Slovakia, Hungary, Romania;
- Eastern Europe 2: Bulgaria, Turkey;
- Eastern Europe 3: Ukraine, Belarus, Lithuania;
- Czech Republic;
- Poland;
- Russia;
- Other: Argentina.

Therefore the covariate “country” will have one category for each region instead of for each single country.

The region/country splits may be amended during the blind data review meetings.

4.12 Protocol Deviations

Major protocol deviations affecting the efficacy analyses may include wrong inclusions, poor compliance and non-permitted concomitant medications. Exact definition of major and minor protocol deviations affecting efficacy will be discussed at the blind data review meetings and documented in the Data Review Report.

The finalisation of protocol violations 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). Deviations will be classified according to the following categories:

- VIOLATION OF INCLUSION CRITERION;

- VIOLATION OF EXCLUSION CRITERION;
- NON ADEQUATE COMPLIANCE TO THE RUN-IN;
- NON ADEQUATE COMPLIANCE TO THE STUDY DRUG;
- 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 Data Review Report.

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.

4.13 Handling of Missing Data

The primary and the key secondary efficacy analyses will be based on the negative binomial model for the moderate and severe asthma exacerbation rate and on linear mixed models for repeated measures for all the other variables. Of note, only asthma exacerbations with onset during the randomised treatment period, i.e. start date ≥ date of start of randomised treatment period and ≤ min(date of completion/discontinuation, date of Visit 7 or study termination visit), will be included in the analysis.. 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[3].

Sensitivity analyses will be conducted to investigate the robustness of the conclusions of the study. A detailed description of these analyses is provided in sections 4.7.1 and 4.7.2.

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:

- for start date and stop date, the first day of the month will be assumed;

- if the month of start date or stop date is missing, January 1st will be assumed.

In order to calculate duration of asthma disease, the following rules will be applied for partial dates of first asthma diagnosis:

- 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 asthma exacerbation, the following rules will be applied for the partial dates of last documented asthma exacerbation:

- if only the day is missing, the first day of the month will be assumed;
- if the month of start date is missing, January 1st will be assumed.

For ACQ-7 questionnaire, the total score will be calculated only if all the seven items are recorded.

A minimum of 7 days with available measurements will be required in each inter-visit period (including run-in period) and in the entire treatment period to consider the following variables as non-missing: average morning and evening PEF, average use of rescue medication, average asthma symptoms scores, percentage of asthma control days, percentage of rescue medication-free days, percentage of asthma symptom-free days.

The derived morning and evening "Best PEF" for the statistical analysis will be calculated only for morning and evening sessions, respectively, recorded pre-dose and with at least two PEF measurements with quality = "GOOD".

For daily use of rescue medication calculation, if one of the two sessions (evening or morning) associated with the day is missing, the daily use of rescue medication in that day will be calculated using the available session only.

For daily asthma symptoms scores, if one of the two sessions (evening or morning) associated with the day is missing, the daily symptom score will be calculated on the available session only. If the two sessions are missing, the day is not considered.

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.

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

In case of partial onset date of asthma 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 asthma exacerbation and in the algorithm defined below for the calculation of the duration of the treatment of an asthma exacerbation with systemic corticosteroids.

In case of emergency room admission for asthma 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 an asthma exacerbation with systemic corticosteroids, the following rules will be applied (considering the date of start and stop of asthma exacerbations before grouping the asthma exacerbations to be considered as a single episode):

- in case of completely missing treatment start date, the asthma 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 ≤ asthma 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, asthma exacerbation start date).
- in case of completely missing treatment stop date, the asthma 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 4.7.1.2);
- 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 ≥ asthma 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, asthma exacerbation stop date).

For FEV_1 and FVC, if one of the lung function measurements at 45 min and 15 min pre-dose is not available, then the non-missing measurement will be taken as the pre-dose value. If no measurement is available, then the pre-dose value will be considered as missing.

In case of less than two missing values among post-dose lung function measurements at 15 min, 30 min, 60 min, 120 min, 180 min, the peak FEV_1 value will be calculated as the maximum of the available values. In case of two or more missing values, the peak FEV_1 value will be considered as missing.

In the calculation of FEV_1 $AUC_{0\text{-}3h}$ normalised by time, missing values will be replaced as follows:

- If the pre-dose value is not available, the entire curve will be considered as missing

- Single, isolated missing values (not pre-dose or last value) will be replaced by linear interpolation using the adjacent values
- If two or more consecutive post-dose time points have a missing observation, the FEV_1 $AUC_{0\text{-}3h}$ will be missing.
- If in total three or more of the post-dose time points have missing values, the FEV_1 $AUC_{0\text{-}3h}$ will be considered as missing.

In the responder analyses, patients with missing data at the relevant time points will 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 all treatment groups with available baseline value in the ITT 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:

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

Other critical missing data, if any, will be discussed during the review of the data. Decisions will be fully documented in the Data Review Report.

4.14 Deviations from SAP

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

4.15 Changes in Conduct or Planned Analyses from the Protocol

- In the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02, the following treatment groups will be compared: CHF 5993 pMDI + CHF 5993 pMDI HS vs. CHF 1535 pMDI + CHF 1535 pMDI HS (see section 4.7.2.3 for further details).
- FEV_1 $AUC_{0\text{-}3h}$ normalised by time at all clinical visits will be analysed as change from baseline for consistency with the other lung function variables.
- All the variables derived from diary data (PEF, rescue use and asthma symptoms) will be evaluated as changes from baseline in each inter-visit period, over the 26-week treatment period (i.e., up to Week 26) and over the 52 week-treatment period.
- The following secondary efficacy variables have been added:
    - FEV_1 response (change from baseline in pre-dose $FEV_1 \geq 100$ ml) at Week 26 and Week 52;

  - ACQ response (change from baseline in ACQ-7 score ≤ - 0.5) at Week 26 and Week 52;
  - Change from baseline in the percentage of rescue medication-free days in each inter-visit period, over the 26-week treatment period and over the 52-week treatment period;
  - Change from baseline in the percentage of asthma symptom-free days in each inter-visit period, over the 26-week treatment period and over the 52-week treatment period;
  - Moderate and severe asthma exacerbation rate over the 52-week treatment period in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02;
  - Time to first moderate or severe asthma exacerbation in the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02.

- CS abnormal findings in the 24-hour ECG Holter were already to be reported as AEs. Therefore, a separate summary for these findings was not presented. Instead, the following variables derived from 24-hour ECG Holter were summarised using descriptive statistics: minimum and maximum HR, longest and fastest tachycardia duration, longest and fastest tachycardia maximum HR, longest and slowest bradycardia duration, longest and slowest bradycardia minimum HR, time in Atrial Fibrillation percentage, Atrial Fibrillation peak average rate, supraventricular total, ventricular total and number of RR > 2 sec.

4.16 Algorithms/SAS Codes

Note: the SAS code for the pooled analyses will be similar to the one included below for the present study.

- **Tables that need descriptive statistics – continuous variables:**

PROC UNIVARIATE DATA=dset NOPRINT;
VAR var1 var2 var3 …varn;
BY byvar; (optional)
OUTPUT OUT=outname
*N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std *Q1=q1 Q3=q3; *Include Q1 and Q3 for EQ-5D-3L data only;*
RUN;

- **Tables that need frequency counts:**

PROC FREQ DATA=dset NOPRINT;
BY byvar; (optional)
*TABLES var1*var2;*
OUTPUT OUT=outname;
RUN;

- **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 3.9999999 11.9999999 25.9999999 39.9999999 51.99999999 EoT) alpha=.05 outsurv=estim reduceout;
*TIME time*event(0);*
STRATA tmt / test=logrank;
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 >52 weeks (if any).
- note: log-rank test will be performed separately for each pairwise comparison.

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

```
PROC PHREG data=dataset;
    CLASS tmt country n_asthma_exac;
    MODEL time*event(0) = tmt country n_asthma_exac / ties=exact;
    CONTRAST 'a vs b' tmt 1 -1 0 / estimate=exp;
    CONTRAST 'a vs c' tmt 1 0 -1 / estimate=exp;
    CONTRAST 'c vs b' tmt 0 -1 1 / estimate=exp;
RUN;
```

Notes:

- Tmt represents the treatment group;
- Country represents the region (pre-defined pooled countries);
- n_asthma_exac represents the number of asthma exacerbations in the last year (classified into 2 groups: 1 or >1);
- Time represents the time to event or time to censoring;
- Event represents the censoring indicator (0 = censored);
- Treatment order: 1 = CHF 5993 pMDI HS, 2 = CHF 1535 pMDI HS, 3 = CHF 1535 pMDI HS + Tiotropium;
- 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 GENMOD data = dataset;
    CLASS tmt country;
    MODEL response = tmt country baseline / dist=binomial wald type3;
    ESTIMATE 'A vs B' tmt 1 -1 0 / exp;
    ESTIMATE 'A vs C' tmt 1 0 -1 / exp;
    ESTIMATE 'C vs B' tmt 0 -1 1 / exp;
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 region (pre-defined pooled countries);
- Baseline represents the baseline value of the variable;
- Treatment order: 1 = CHF 5993 pMDI HS, 2 = CHF 1535 pMDI HS, 3 = CHF 1535 pMDI HS + Tiotropium.

- **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 asthma exacerbations during the randomised treatment period, analysed using a negative binomial model, and ANCOVA 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 7) 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	A	X	X	1	.
1	A	X	X	2	.
1	A	X	X	3	X
1	A	X	X	4	X
1	A	X	X	5	X
2	B	X	X	1	.
2	B	X	X	2	.
2	B	X	X	3	X
3	A	X	X	1	.
3	A	X	X	2	.
3	A	X	X	3	X
3	A	X	X	4	.
3	A	X	X	5	X
4	B	X	X	1	.
4	B	X	X	2	.
5	A	.	X	1	.
5	A	.	X	2	.
5	A	.	X	3	X

Step 1 (visits 1 and 2 not selected since 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	A	X	X	3	X
1	A	X	X	4	X
1	A	X	X	5	X
2	B	X	X	3	X
3	A	X	X	3	X
3	A	X	X	4	.
3	A	X	X	5	X

Step 2 (added records in *italic*):

Patient	Treatment	Covariate	Baseline	Visit	Change from baseline
1	A	X	X	3	X
1	A	X	X	4	X
1	A	X	X	5	X
2	B	X	X	3	X
2	*B*	*X*	*X*	*4*	.
2	*B*	*X*	*X*	*5*	.
3	A	X	X	3	X
3	A	X	X	4	.
3	A	X	X	5	X

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

PROC GENMOD data = dataset;
CLASS tmt country n_asthma_exac;
MODEL count = tmt country n_asthma_exac / offset=log_years dist=negbin wald type3;
LSMEANS tmt / om cl exp;
ESTIMATE 'A vs B' tmt 1 -1 0 / exp;
ESTIMATE 'A vs C' tmt 1 0 -1 / exp;
ESTIMATE 'C vs B' tmt 0 -1 1 / exp;
RUN;

Notes:
- Count represents the total number of asthma exacerbations for each patient;
- Tmt represents the treatment group;
- Country represents the region (pre-defined pooled countries);
- n_asthma_exac represents the number of asthma exacerbations in the last year (classified into 2 groups: 1 or >1);
- log_years represents the logarithm of the follow-up time in years;
- Treatment order: 1 = CHF 5993 pMDI HS, 2 = CHF 1535 pMDI HS, 3 = CHF 1535 pMDI HS + Tiotropium.

- **Tables that require linear mixed model for repeated measures for spirometry (pre-dose), ACQ-7, 12-lead ECG (pre-dose) and 95/90% CIs of differences between treatments:**

```
PROC MIXED data = dataset;
    CLASS tmt visit country patient;
    MODEL change = tmt visit tmt*visit country baseline baseline*visit / ddfm=kr;
    REPEATED visit / subject=patient type=un;
    LSMEANS tmt*visit / om at means cl; *add "alpha=0.1" for ECG;
    LSMESTIMATE tmt*visit
        'A vs B: Week 4'    1 0 0 0 0 -1 0 0 0 0 0 0 0 0 0,
        'A vs B: Week 12'   0 1 0 0 0 0 -1 0 0 0 0 0 0 0 0,
        'A vs B: Week 26'   0 0 1 0 0 0 0 -1 0 0 0 0 0 0 0,
        'A vs B: Week 40'   0 0 0 1 0 0 0 0 -1 0 0 0 0 0 0,
        'A vs B: Week 52'   0 0 0 0 1 0 0 0 0 -1 0 0 0 0 0,
        'A vs C: Week 4'    1 0 0 0 0 0 0 0 0 0 -1 0 0 0 0,
        'A vs C: Week 12'   0 1 0 0 0 0 0 0 0 0 0 -1 0 0 0,
        'A vs C: Week 26'   0 0 1 0 0 0 0 0 0 0 0 0 -1 0 0,
        'A vs C: Week 40'   0 0 0 1 0 0 0 0 0 0 0 0 0 -1 0,
        'A vs C: Week 52'   0 0 0 0 1 0 0 0 0 0 0 0 0 0 -1,
        'C vs B: Week 4'    0 0 0 0 0 -1 0 0 0 0 1 0 0 0 0,
        'C vs B: Week 12'   0 0 0 0 0 0 -1 0 0 0 0 1 0 0 0,
        'C vs B: Week 26'   0 0 0 0 0 0 0 -1 0 0 0 0 1 0 0,
        'C vs B: Week 40'   0 0 0 0 0 0 0 0 -1 0 0 0 0 1 0,
        'C vs B: Week 52'   0 0 0 0 0 0 0 0 0 -1 0 0 0 0 1 / cl;*add "alpha=0.1" for ECG;
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 region (pre-defined pooled countries);
- Baseline represents the baseline value of the variable;
- Patient represents the Patient Number;
- Treatment order: 1 = CHF 5993 pMDI HS, 2 = CHF 1535 pMDI HS, 3 = CHF 1535 pMDI HS + Tiotropium.

- **Tables that require linear mixed model for repeated measures for post-dose spirometry (FEV_1 peak and AUC) and 12-lead ECG and 95/90% CIs of differences between treatments:**

```
PROC MIXED data = dataset;
    CLASS tmt visit country patient;
    MODEL change = tmt visit tmt*visit country baseline baseline*visit / ddfm=kr;
    REPEATED visit / subject=patient type=un;
    LSMEANS tmt*visit / om at means cl; *add "alpha=0.1" for ECG;
    LSMESTIMATE tmt*visit
        'A vs B: Week 0'   1 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0,
        'A vs B: Week 4'   0 1 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0,
        'A vs B: Week 12'  0 0 1 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0,
        'A vs B: Week 26'  0 0 0 1 0 0 0 0 0 -1 0 0 0 0 0 0 0 0,
        'A vs B: Week 40'  0 0 0 0 1 0 0 0 0 0 -1 0 0 0 0 0 0 0,
        'A vs B: Week 52'  0 0 0 0 0 1 0 0 0 0 0 -1 0 0 0 0 0 0,
        'A vs C: Week 0'   1 0 0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0,
        'A vs C: Week 4'   0 1 0 0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0,
        'A vs C: Week 12'  0 0 1 0 0 0 0 0 0 0 0 0 0 0 -1 0 0 0,
        'A vs C: Week 26'  0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 -1 0 0,
        'A vs C: Week 40'  0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 -1 0,
        'A vs C: Week 52'  0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 -1,
        'C vs B: Week 0'   0 0 0 0 0 0 -1 0 0 0 0 0 1 0 0 0 0 0,
        'C vs B: Week 4'   0 0 0 0 0 0 0 -1 0 0 0 0 0 1 0 0 0 0,
        'C vs B: Week 12'  0 0 0 0 0 0 0 0 -1 0 0 0 0 0 1 0 0 0,
        'C vs B: Week 26'  0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 1 0 0,
        'C vs B: Week 40'  0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 1 0,
        'C vs B: Week 52'  0 0 0 0 0 0 0 0 0 0 0 -1 0 0 0 0 0 1 / cl;*add "alpha=0.1" for
    ECG;
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 region (pre-defined pooled countries);
- Baseline represents the baseline value of the variable;
- Patient represents the Patient Number;
- Treatment order: 1 = CHF 5993 pMDI HS, 2 = CHF 1535 pMDI HS, 3 = CHF 1535 pMDI HS + Tiotropium;.

- **Tables that require ANCOVA model for changes from pre-dose to post-dose for 12-lead ECG and 90% CIs of differences between treatments:**

```
PROC MIXED data = dataset;
    BY visit;
    CLASS tmt country;
    MODEL change = tmt country predose;
    LSMEANS tmt / om cl alpha=0.1;
    LSMESTIMATE tmt
        'A vs B 1 -1 0,
        'A vs C' 1 0 -1,
        'C vs B' 0 -1 1 / cl alpha=0.1;
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 region (pre-defined pooled countries);
- Predose represents the pre-dose value of the variable at each visit;
- Treatment order: 1 = CHF 5993 pMDI HS, 2 = CHF 1535 pMDI HS, 3 = CHF 1535 pMDI HS + Tiotropium.

- **Tables that require linear mixed model for repeated measures for diary data (PEF data, rescue medication, asthma symptoms) and 95% CIs of differences between treatments:**

```
PROC MIXED data = dataset;
    CLASS tmt visit country patient;
    MODEL change = tmt visit tmt*visit country 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 0 -1 0 0 0 0 0 0 0 0 0,
        'A vs B: Week 12'   0 1 0 0 0 0 -1 0 0 0 0 0 0 0 0,
        'A vs B: Week 26'   0 0 1 0 0 0 0 -1 0 0 0 0 0 0 0,
        'A vs B: Week 40'   0 0 0 1 0 0 0 0 -1 0 0 0 0 0 0,
        'A vs B: Week 52'   0 0 0 0 1 0 0 0 0 -1 0 0 0 0 0,
        'A vs C: Week 4'    1 0 0 0 0 0 0 0 0 0 -1 0 0 0 0,
        'A vs C: Week 12'   0 1 0 0 0 0 0 0 0 0 0 -1 0 0 0,
        'A vs C: Week 26'   0 0 1 0 0 0 0 0 0 0 0 0 -1 0 0,
        'A vs C: Week 40'   0 0 0 1 0 0 0 0 0 0 0 0 0 -1 0,
        'A vs C: Week 52'   0 0 0 0 1 0 0 0 0 0 0 0 0 0 -1,
        'C vs B: Week 4'    0 0 0 0 0 -1 0 0 0 0 1 0 0 0 0,
        'C vs B: Week 12'   0 0 0 0 0 0 -1 0 0 0 0 1 0 0 0,
        'C vs B: Week 26'   0 0 0 0 0 0 0 -1 0 0 0 0 1 0 0,
        'C vs B: Week 40'   0 0 0 0 0 0 0 0 -1 0 0 0 0 1 0,
        'C vs B: Week 52'   0 0 0 0 0 0 0 0 0 -1 0 0 0 0 1,
        'A: Over 26 Weeks'  4 8 14 0 0 0 0 0 0 0 0 0 0 0 0 divisor=26,
        'B: Over 26 Weeks'  0 0 0 0 0 4 8 14 0 0 0 0 0 0 0 divisor=26,
        'C: Over 26 Weeks'  0 0 0 0 0 0 0 0 0 0 4 8 14 0 0 divisor=26
        'A vs B: Over 26 Weeks' 4 8 14 0 0 -4 -8 -14 0 0 0 0 0 0 0 divisor=26,
        'A vs C: Over 26 Weeks' 4 8 14 0 0 0 0 0 0 0 -4 -8 -14 0 0 divisor=26,
        'C vs B: Over 26 Weeks' 0 0 0 0 0 -4 -8 -14 0 0 4 8 14 0 0 divisor=26,
        'A: Over 52 Weeks'  4 8 14 14 12 0 0 0 0 0 0 0 0 0 0 divisor=52,
        'B: Over 52 Weeks'  0 0 0 0 0 4 8 14 14 12 0 0 0 0 0 divisor=52,
        'C: Over 52 Weeks'  0 0 0 0 0 0 0 0 0 0 4 8 14 14 12 divisor=52
        'A vs B: Over 52 Weeks' 4 8 14 14 12 -4 -8 -14 -14 -12 0 0 0 0 0 divisor=52,
        'A vs C: Over 52 Weeks' 4 8 14 14 12 0 0 0 0 0 -4 -8 -14 -14 -12 divisor=52,
        'C vs B: Over 52 Weeks' 0 0 0 0 0 -4 -8 -14 -14 -12 4 8 14 14 12 divisor=52
                                                                / 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 region (pre-defined pooled countries);
- Baseline represents the baseline value of the variable;
- Patient represents the Patient Number;

– Treatment order: 1 = CHF 5993 pMDI HS, 2 = CHF 1535 pMDI HS, 3 = CHF 1535 pMDI HS + Tiotropium.

- **Multiple Imputation for the Sensitivity Analyses of the Change from Baseline in pre-dose FEV_1**

An example of SAS code is provided below for the sensitivity analyses of pre-dose FEV_1. It will be adapted for peak FEV_1 and average morning PEF.

Preliminary step

Imputation based on the MAR assumption using the joint modelling approach in order to obtain monotone missing data patterns.

```
PROC MI DATA=dataset OUT=monotone NIMPUTE=1000 SEED=382319321 NOPRINT;
    VAR tmt_d1 tmt_d2 country_d1-country_dx pb_FEV1_visit1 visit2-visit7;
     MCMC CHAIN=MULTIPLE IMPUTE=MONOTONE;
RUN;
```

Notes:

- dataset includes one record per patient and is sorted by patient;
- tmt_d1 and tmt_d2 represent the dummy variables for treatment group (values of the dummy variables: 0,0 for CHF 5993 pMDI HS; 1,0 for CHF 1535 pMDI HS; 0,1 for CHF 1535 pMDI HS + Tiotropium);
- country_d1-country_dx represent the dummy variables for the region (pre-defined pooled countries) (values of the dummy variables: 1,0,0,0,0,0,0 for Western Europe; 0,1,0,0,0,0,0 for Eastern Europe 1; 0,0,1,0,0,0,0 for Eastern Europe 2; 0,0,0,1,0,0,0 for Eastern Europe 3; 0,0,0,0,1,0,0 for Czech Republic; 0,0,0,0,0,1,0 for Poland; 0,0,0,0,0,0,1 for Russia; 0,0,0,0,0,0,0 for Other: Argentina);
- *pb_FEV1_ visit1* represent pre-bronchodilator FEV_1 value at Visit 1;
- visit2-visit7 represent the pre-dose FEV_1 measurements at Visits 2 to 7.

Missing at random imputation

```
PROC MI DATA=monotone OUT=imputed_mar NIMPUTE=1 SEED=382319321
        NOPRINT;
    BY _Imputation_;
    CLASS tmt country;
    VAR tmt country pb_FEV1_visit1 visit2-visit7;
    MONOTONE REGRESSION;
RUN;
```

Notes:

- tmt represents the treatment group (treatment order: 1 = CHF 5993 pMDI HS, 2 = CHF 1535 pMDI HS, 3 = CHF 1535 pMDI HS + Tiotropium);
- country represents the region (pre-defined pooled countries);
- *pb_FEV1_ visit1* represent pre-bronchodilator FEV_1 value at Visit 1;
- visit2-visit7 represent the pre-dose FEV_1 measurements at Visits 2 to 7.

Copy reference imputation

```
PROC MI DATA=monotone OUT=imputed_cr NIMPUTE=1 SEED=382319321
        NOPRINT;
    BY _Imputation_;
    CLASS tmt country;
    VAR country pb_FEV1_visit1 visit2-visit7;
    MONOTONE REGRESSION;
    MNAR MODEL (visit3-visit7 / MODELOBS=(tmt='CHF 5993 pMDI HS'));
RUN;
```

Notes:

- tmt represents the treatment group (treatment order: 1 = CHF 5993 pMDI HS, 2 = CHF 1535 pMDI HS, 3 = CHF 1535 pMDI HS + Tiotropium);
- country represents the region (pre-defined pooled countries);
- *pb_FEV1_ visit1* represent pre-bronchodilator FEV_1 value at Visit 1;
- visit2-visit7 represent the pre-dose FEV_1 measurements at Visits 2 to 7.

BOCF-like imputation

```
DATA imputed_bocf1;
    SET monotone;
    visit=2;
    value=visit2;
    OUTPUT;
    value=.;
    ARRAY v[*] visit3-visit7;
    DO visit=3 TO 7;
       IF v[visit-2]=. THEN OUTPUT;
    END;
RUN;

PROC MI DATA=imputed_bocf1 OUT=imputed_bocf2 NIMPUTE=1 SEED=382319321
        NOPRINT;
    BY _Imputation_;
    CLASS country;
    VAR country pb_FEV1_visit1 value;
    MONOTONE REGRESSION;
RUN;

PROC TRANSPOSE DATA=imputed_bocf2 OUT=imputed_bocf3 PREFIX=visit_bocf;
    BY _Imputation_ patient;
    ID visit;
    VAR value;
RUN;

DATA imputed_bocf4;
    MERGE monotone imputed_bocf3;
    BY _Imputation_ patient;
```

```
    ARRAY v[*] visit2-visit7;
    ARRAY vb[*] visit_bocf2-visit_bocf7;
    DO i=1 TO 6;
      IF v[i]=. THEN v[i]=vb[i];
    END;
RUN;
```

Notes:

- tmt represents the treatment group (treatment order: 1 = CHF 5993 pMDI HS, 2 = CHF 1535 pMDI HS, 3 = CHF 1535 pMDI HS + Tiotropium);
- country represents the region (pre-defined pooled countries);
- *pb_FEV1_ visit1* represent pre-bronchodilator FEV_1 value at Visit 1;
- visit2-visit7 represent the pre-dose FEV_1 measurements at Visits 2 to 7.

Analysis step

The imputed dataset obtained using the above SAS code will be finally analysed and the results will be combined.

```
DATA m_mian01 (DROP= visit3-visit7 i RENAME=visit2=baseline);
    SET imputed_xxx;
    ARRAY v[*] visit3-visit7;
DO i=1 TO 5;
      visit=i+2;
      change=v[i]-visit2;
      OUTPUT;
    END;
RUN;

PROC SORT DATA=m_mian01 OUT=m_mian01s;
    BY visit _Imputation_ patient;
RUN;

ODS OUTPUT LSMEANS=m_mian02 ESTIMATES=m_mian03;
PROC MIXED DATA=m_mian01s;
    BY visit _Imputation_;
    CLASS tmt country;
    MODEL change = tmt country baseline;
    LSMEANS tmt / om cl;
    ESTIMATE 'A vs B' tmt 1 -1 0 / cl;
    ESTIMATE 'A vs C' tmt 1 0 -1 / cl;
    ESTIMATE 'C vs B' tmt 0 -1 1 / cl;
RUN;
ODS OUTPUT CLOSE;

PROC MIANALYZE PARMS(CLASSVAR=FULL)=m_mian02;
    BY visit;
```

```
    CLASS tmt;
    MODELEFFECTS tmt;
RUN;

PROC MIANALYZE PARMS(CLASSVAR=FULL)=m_mian03;
    BY visit;
    CLASS tmt;
    MODELEFFECTS tmt;
RUN;
```

Notes:

- imputed_xxx represents an imputed dataset obtained with one of the strategies above defined;
- tmt represents the treatment group (treatment order: 1 = CHF 5993 pMDI HS, 2 = CHF 1535 pMDI HS, 3 = CHF 1535 pMDI HS + Tiotropium);
- country represents the region (pre-defined pooled countries);
- visit2-visit7 represent the pre-dose FEV_1 measurements at Visits 2 to 7;
- baseline represents the baseline value of the variable;
- patient represents the patient number.

- **Multiple Imputation for asthma exacerbation rate**

An example of SAS code is provided below for the sensitivity analyses of moderate and severe asthma exacerbation rate.

Missing at random and copy reference imputation

```
PROC GENMOD DATA=dataset1;
    MODEL count = tmt_d1 tmt_d2 country_d1-country_dx n_asthma_exac /
    OFFSET=log_years DIST=NEGBIN;
    /* >1000 imputations since some will be discarded due to convergence issues with the
    model */
    BAYES NBI=1000 NMC=11000 THIN=10 OUTPOST=dataset2 SEED=34783129;
RUN;

DATA dataset3;
        SET dataset2;
        RENAME tmt_d1-tmt_d2=c_tmt_d1-c_tmt_d2
                    country_d1-country_dx=c_country_d1-c_country_dx
                    n_asthma_exac_d=c_n_asthma_exac_d;
RUN;

PROC SQL;
        CREATE TABLE dataset4 AS
        SELECT dataset1.*, dataset3.*
        FROM dataset1, dataset3
ORDER BY Iteration, patient;
        ;
QUIT;
```

```
DATA dataset5;
      SET dataset4;
      ARRAY c[*] c_country_d1-c_country_dx c_n_asthma_exac_d;
      ARRAY x[*] country_d1-country_dx n_asthma_exac_d;
      k=1/Dispersion;
      imp_subj=(years<365/365.25);
      years_imp=MAX(years,365/365.25);
      log_years_imp=LOG(years_imp);
      linpred_1=.;
      IF imp_subj THEN DO;
          years_miss=years_imp-years;
          linpred_1=Intercept;
          DO i=1 TO DIM(c);
              linpred_1+c[i]*x[i];
          END;
          linpred_mar=linpred_1+c_tmt_d1*tmt_d1+c_tmt_d2*tmt_d2;
          linpred_cr=linpred_1;
          y1hat_mar=years*EXP(linpred_mar);
          y2hat_mar=years_miss*EXP(linpred_mar);
          y1hat_cr=years*EXP(linpred_cr);
          y2hat_cr=years_miss*EXP(linpred_cr);
          CALL STREAMINIT(3231212);
          y2_mar=RAND('NEGBINOMIAL',(k+y1hat_mar)/(k+y1hat_mar+y2hat_mar),k+
      count);
          y2_cr=RAND('NEGBINOMIAL',(k+y1hat_cr)/(k+y1hat_cr+y2hat_cr),k+count);
          y_imp_mar=count+y2_mar;
          y_imp_cr=count+y2_cr;
      END;
      ELSE DO;
          y_imp_mar=count;
          y_imp_cr=count;
      END;
RUN;
```

Notes:

- dataset1 includes one record per patient and is sorted by patient;
- patient represents the Patient Number;
- count represents the total number of asthma exacerbations observed for each patient;
- tmt represents the treatment group (treatment order: 1 = CHF 5993 pMDI HS, 2 = CHF 1535 pMDI HS, 3 = CHF 1535 pMDI HS + Tiotropium);
- tmt_d1 and tmt_d2 represent the dummy variables for treatment group (values of the dummy variables: 0,0 for CHF 5993 pMDI HS; 1,0 for CHF 1535 pMDI HS; 0,1 for CHF 1535 pMDI HS + Tiotropium);
- country represents the region (pre-defined pooled countries);
- country_d1-country_dx represent the dummy variables for the region (pre-defined pooled countries) (values of the dummy variables: 1,0,0,0,0,0,0 for Western Europe; 0,1,0,0,0,0,0 for Eastern Europe 1; 0,0,1,0,0,0,0 for Eastern Europe 2; 0,0,0,1,0,0,0 for

Eastern Europe 3; 0,0,0,0,1,0,0 for Czech Republic; 0,0,0,0,0,1,0 for Poland; 0,0,0,0,0,0,1 for Russia; 0,0,0,0,0,0,0 for Other: Argentina); ;

- n_asthma_exac represents the number of asthma exacerbations in the last year (classified into 2 groups: 1 or >1);
- n_asthma_exac_d represents the dummy variable for number of asthma exacerbations in the last year;
- log_years represents the logarithm of the follow-up time in years.

Analysis step

The imputed dataset obtained using the above SAS code will be finally analysed and the results will be combined.

```
ODS OUTPUT LSMeans=lsmeans1 Estimates=ratios1;
PROC GENMOD DATA=dataset5;
        BY Iteration;
        CLASS tmt country n_asthma_exac;
        /* MAR imputation */
        MODEL y_imp_mar = tmt country n_asthma_exac
        / OFFSET=log_years_imp DIST=NEGBIN;
        /* Alternative MODEL statement: copy reference imputation */
        MODEL y_imp_cr = tmt country n_asthma_exac
        / OFFSET=log_years_imp DIST=NEGBIN;
        LSMEANS tmt / OM;
        ESTIMATE 'A vs B' tmt 1 -1 0;
        ESTIMATE 'A vs C' tmt 1 0 -1;
        ESTIMATE 'C vs B' tmt 0 -1 1;
RUN;

DATA lsmeans2;
        SET lsmeans1 (WHERE=(zValue ne .));
        BY Iteration;
        IF first.Iteration THEN _Imputation_+1;
        IF _Imputation_ LE 1000;
RUN;

ODS OUTPUT ParameterEstimates=lsmeans3;
PROC MIANALYZE PARMS=lsmeans2;
        CLASS tmt;
        MODELEFFECTS tmt;
RUN;
```

```
DATA lsmeans4;
        SET lsmeans3;
        exp_est=EXP(Estimate);
        exp_lcl=EXP(LCLMean);
        exp_ucl=EXP(UCLMean);
RUN;

DATA ratios2 (RENAME=LBetaEstimate=Estimate);
        SET ratios1 (WHERE=(ChiSq ne .));
        BY Iteration;
        IF first.Iteration THEN _Imputation_+1;
        IF _Imputation_ LE 1000;
        Effect='Label';
RUN;

ODS OUTPUT ParameterEstimates=ratios3;
PROC MIANALYZE PARMS =ratios2;
        CLASS Label;
        MODELEFFECTS Label;
RUN;

DATA ratios4;
        SET ratios3;
        exp_est=EXP(Estimate);
        exp_lcl= EXP (LCLMean);
        exp_ucl= EXP (UCLMean);
RUN;
```

5 Tables and Listings

5.1 Output Format

All output will be produced using SAS version 9.4 or a later version.

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* or *population* 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.

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.

A *landscape layout* is proposed for both table and listing presentations.

Tables and listings will be produced in rich text (RTF) format (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. *Header and footer* will be both 1.27 cm.

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.

Figures will be produced in rich text (RTF) format. The resolution should be set using the option IMAGE_DPI=400.

A portrait layout should be considered for the document with all figures.

Titles and footnote will not be included in the body of figure.

The size of the figure (except forest plot) will be: width=16.3 cm height=12.2 cm (this option will be included in the ODS GRAPHICS ON statement).

The size of forest plot figure will be: width=16.3 cm height=20 cm (this option will be included in the ODS GRAPHICS ON statement).

5.2 Quality Control of Outputs

The following steps will be taking 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 and figures will be independently programmed form the raw datasets by a second statistician/programmer and outputs will be compared either electronically (by

comparing the data being tabulated using PROC COMPARE) or by manually comparing the data in the 2 independent outputs.

- Listings will be checked either electronically (by comparing the data being listed using PROC COMPARE) or by manually comparing the data in the listings to the raw/derived data.
- 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, except for the cases described in

Table 1: Baseline calculation**s**):

- BMI (kg/m^2), duration of smoking (years), duration of asthma disease (years), time since last documented asthma exacerbation (months), duration of the treatment of asthma exacerbations with systemic steroids, duration of hospitalisation for asthma exacerbations (days), average pre-dose morning/evening PEF, exposure (days), duration of AE (days): whole numbers;
- time to discontinuation (weeks), compliance, time to first asthma exacerbation (weeks), average use of rescue medication (daily mean number of puffs), percentage of rescue medication-free days, daily asthma symptoms scores, percentage of asthma symptom free-days, percentage of asthma control days: 1 decimal place;
- EQ-5D-3L index, peak FEV_1, FEV_1 $AUC_{0\text{-}3h}$: 2 decimal places;
- change from baseline/ 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;
- 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: 2 decimal places;

- rates related to MACEs: 1 decimal place;
- total follow-up time in the tables on MACEs: 1 decimal place.

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

- individual follow-up time (years): 3 decimal places;
- individual rate (per year): 1 decimal place;
- total follow-up time (years): 1 decimal place;
- rate (per patient per year, unadjusted and adjusted), adjusted rate ratio and its confidence limits: 2 decimal places.

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.

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

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

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

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

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 treatment group, patient and visit (unless otherwise specified) and have the study data tabulation model (SDTM) and/or analysis dataset model (ADaM) source data referenced in a footnote. The columns of each listing should fit into one page and should not be split into different pages. All tables, listings and figures will be collated into three Microsoft Word complete documents. If the listings are too large to be included in one file they will be separated into manageable sized files. The Microsoft Word documents will be subsequently converted in portable document format (PDF). Both, Word and PDF documents will include a table of contents with hyperlinks.

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

For the pooled analysis of the two pivotal studies CCD-05993AB1-03 and CCD-05993AB2-02, the tables will be presented separately, with a specific numbering starting from

14.2.21.1.1.1. Source listings referenced in footnote will not be needed, as they will be already provided for both studies.

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Tables and figures (defined in section 5.6) for the pooled analysis will follow the format of the corresponding study-level outputs, but with two treatment groups only.
The two treatment group labels will be as follows:

- CHF 5993 pMDI + CHF 5993 pMDI HS
- CHF 1535 pMDI + CHF 1535 pMDI HS

The footnotes of the tables and figures will be identical, with the exception of the study and program identification footnote, and the source listing number footnote (including the information on the study), which will be displayed as follows:

```
CHIESI FARMACEUTICI S.P.A.: CCD-05993AB1-03/CCD-05993AB2-02/POOLED/CIL-
XX/SHELL/PGNAME.SAS
Produced: Day Month Year Time                                  Page X of Y
Source: CCD-05993AB1-03: Listing x, CCD-05993AB2-02: Listing y
```

With the *PGNAME*.SAS numbered from PSEC01P.SAS (Table 14.2.20.1.1) to PSEC06P.SAS (Table 14.2.20.3.2), from PSEC031P.SAS (Table 14.2.20.4.1) to PSEC038P.SAS (Table 14.2.20.4.6) and from PSEC07P.SAS (Table 14.2.21.1) to PSEC18P.SAS (Table 14.2.25.2) for the tables. And from PSEC01F.SAS to PSEC04F.SAS for the figures.

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Figures for CCD-05993AB1-03 and CCD-05993AB2-02 pooled analysis

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5.7 Appendices

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Tables, Listings, and Figures will follow the format of: .
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6 References

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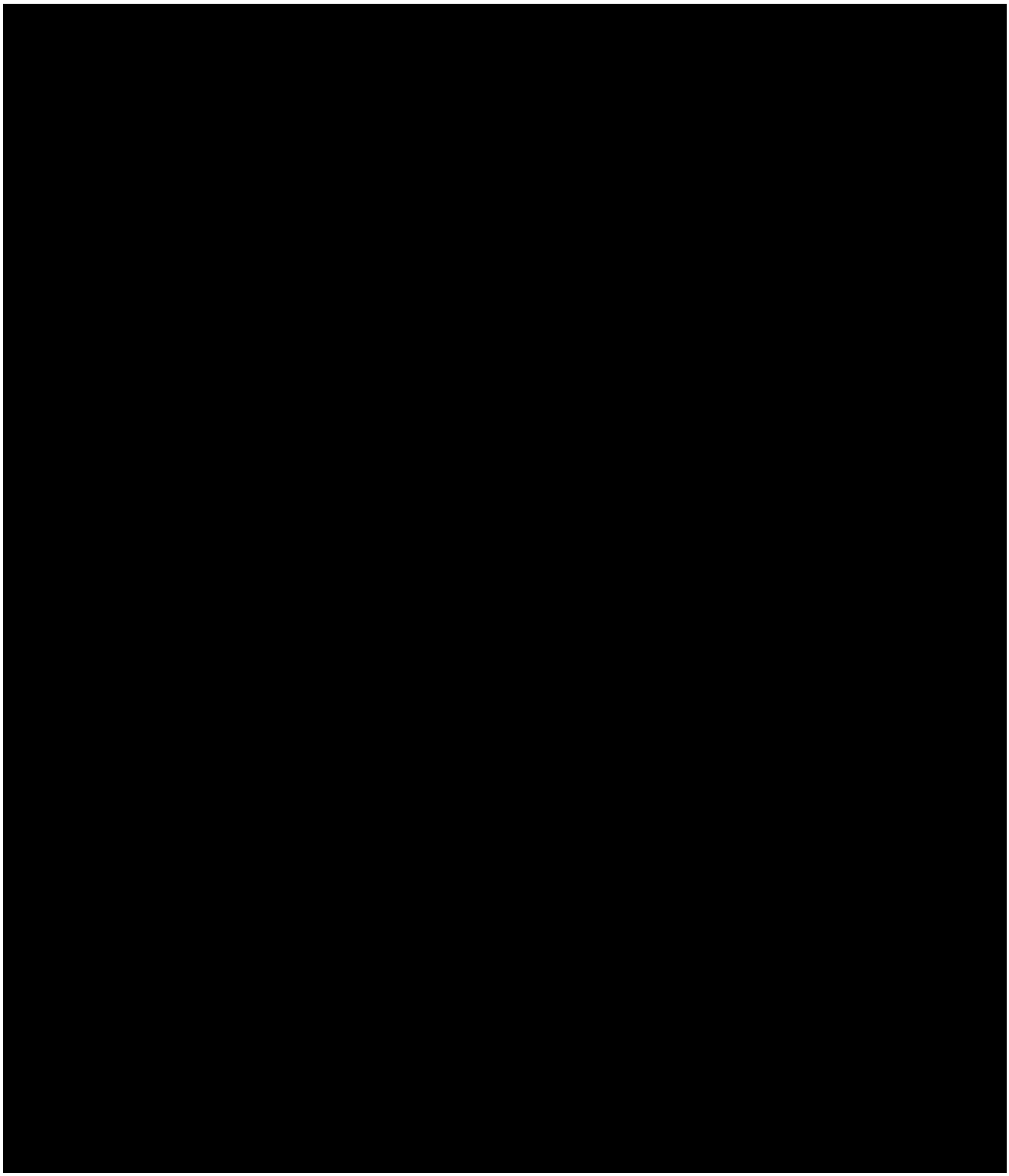
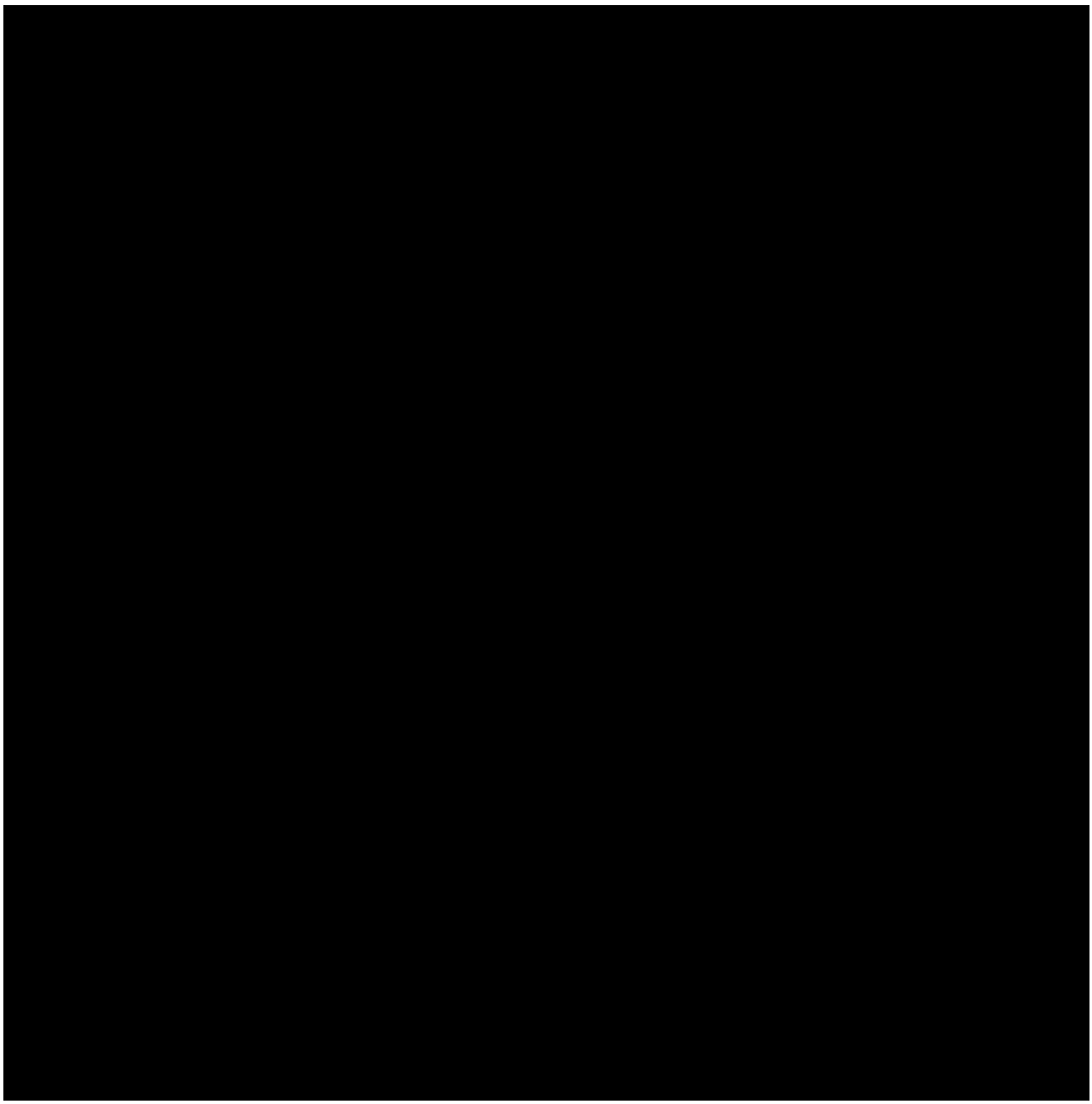
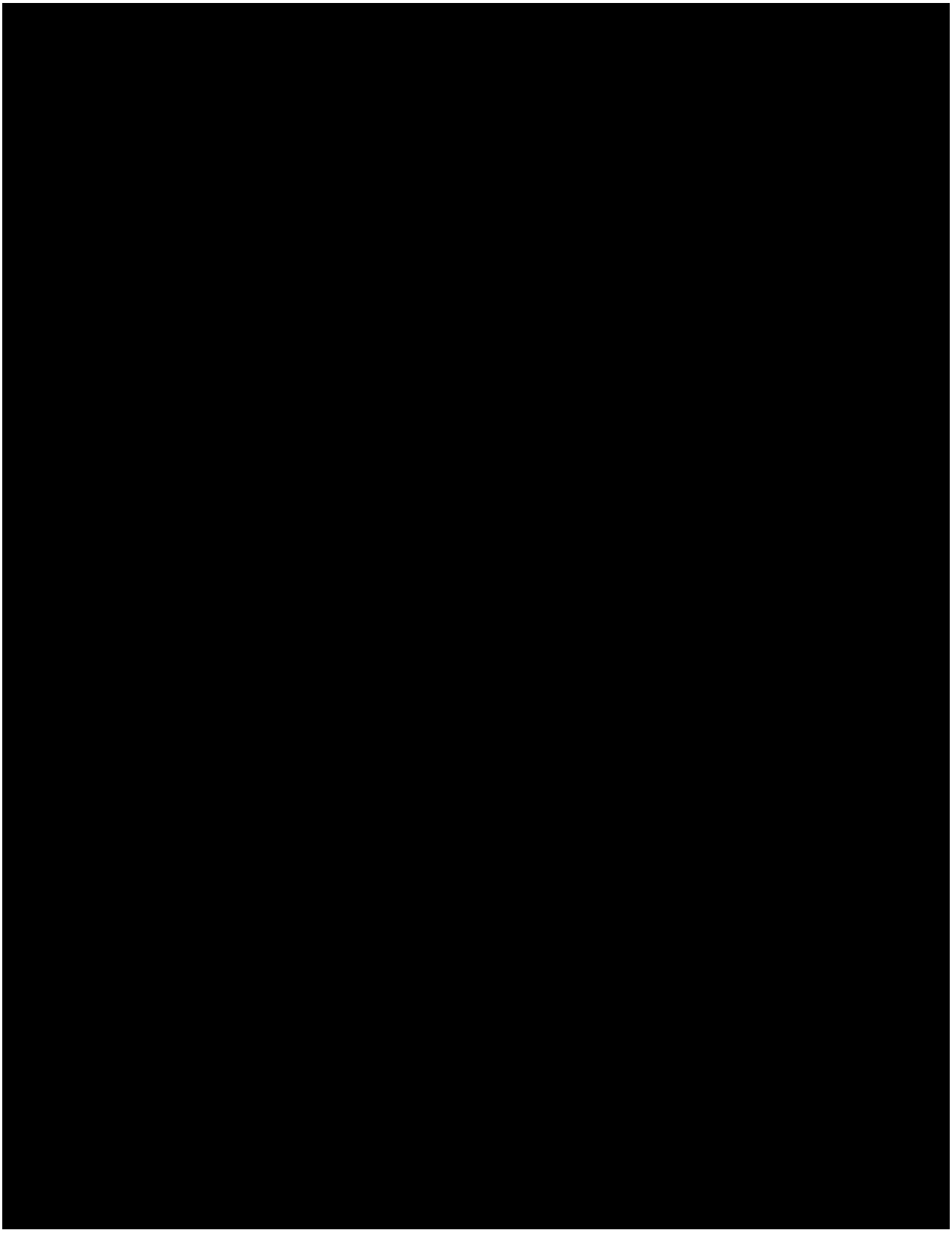
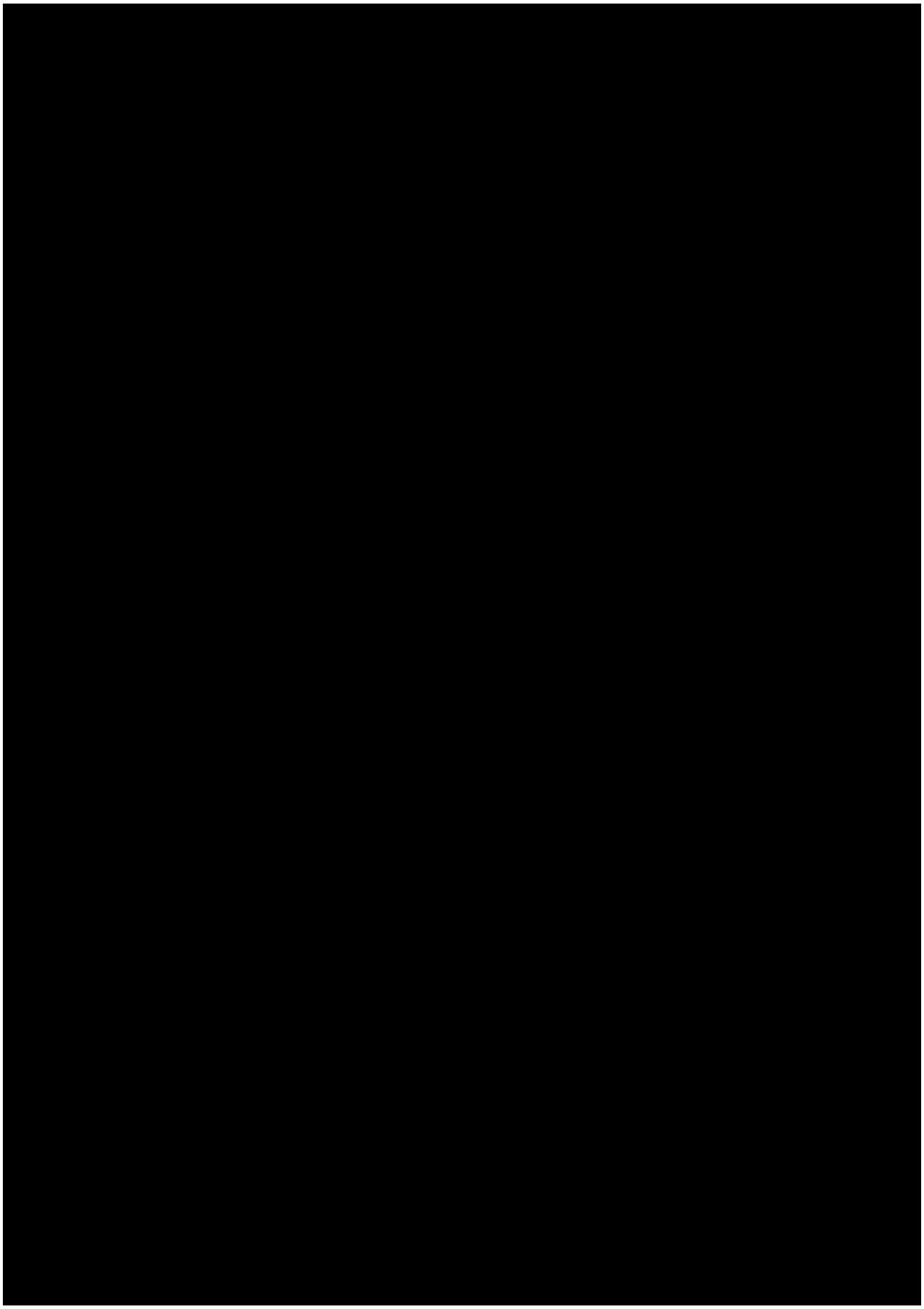
APPENDIX I: ASTHMA CONTROL QUESTIONNAIRE© (ACQ-7)





APPENDIX II: EQ-5D-3L™





Appendix III: EQ-5D-3L algorithm