CHIESI

FLASH

A RANDOMIZED, DOUBLE-BLIND, PLACEBO AND ACTIVE-CONTROLLED, INCOMPLETE BLOCK CROSS-OVER, DOSE RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF 4 DOSES OF CHF 1531 PMDI (FORMOTEROL FUMARATE) IN ASTHMATIC SUBJECTS

Protocol: CCD-05993AA3-03

IND No: 133680

ClinicalTrials.gov ID: NCT03086460

Statistical Analysis Plan

Amendment

FINAL 2.0 Version

11 APR 2019

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1 SOPs to be followed

The statistical analysis will be carried out according to the following [redacted] SOPs:

SOP Number	SOP Title	Effective Date & Version Number	[redacted] or Sponsor
SOP_ST_03	Statistical Analysis Plan	3.0 01AUG2015	[redacted]
SOP_ST_04	SAS Programming, QC and Validation	3.0 21DEC2015	[redacted]
SOP_ST_06	Study Unblinding for Analysis	3.0 12JUN017	[redacted]
SOP_ST_07	Statistical Report	3.0 26JUN2017	[redacted]
SOP_ST_08	Trial Statistics File*	2.0 15APR2014	[redacted]

* TSF SOP in combination with the ToC of Chiesi.

2 Abbreviations

ACQ	Asthma Control Questionnaire
ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	ANalysis of COVAriance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve
bid	Bis in die (twice a day)
BUN	Blood urea nitrogen
CI	Confidence Interval
(e) CRF	(Electronic) Case Report Form
CRO	Contract Research Organization
DBP	Diastolic Blood Pressure
ECG	ElectroCardioGram
FEV_1	Forced Expiratory Volume in the 1st second
FF	Formoterol Fumarate
FVC	Forced Vital Capacity
h	hour
HFA	Hydrofluroalkane
HR	Heart Rate
ICS	Inhaled Corticosteroid
IRT	Interactive Response Technology
ITT	Intention to Treat
L	Liter
LABA	Long Acting β_2 adrenergic receptor agonist
LABD	Long-acting bronchodilators
LAMA	Long Acting Muscarinic Antagonist
µg	Microgram
MAR	Missing at Random
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
min	Minutes
mL	Milliliters
PEF	Peak Expiratory Flow
pMDI	Pressurized Metered Dose Inhaler
PP	Per-Protocol
PR	Time Interval from the beginning of the upslope of the P wave to the beginning of the QRS wave in the ECG
QRS	Time Interval from the end of the PR interval to the end of the S wave in the ECG
QTc	Time interval from the beginning of the QRS complex to the end of the T wave in the ECG (corrected for HR)
QTcF	QT interval corrected for HR using Fridericia's formula
SAP	Statistical Analyis Plan
SAE	Serious Adverse Event
SAMA	Short-Acting Muscarinic Antagonist
SBP	Systolic Blood Pressure

SD	Standard Deviation
TEAE	Treatment Emergent Adverse Events

3 Protocol / Clinical Investigation Plan

This document presents the statistical analysis plan (SAP) for Chiesi Farmaceutici S.p.A., Protocol No. CCD-05993AA3-03: A randomized, double-blind, placebo and active-controlled, incomplete block cross-over, dose ranging study to evaluate the efficacy and safety of 4 doses of CHF 1531 pMDI (Formoterol Fumarate) in asthmatic subjects. This analysis plan is based on the final protocol (version 3.0) dated 31 OCT 2017 and the final electronic case report form (eCRF) (version 3.0) dated 14 NOV 2017. Text copied from Protocol is reported in this document in Italics to avoid unnecessary alterations to text approved in the Protocol.The SAP provides the description of the final analyses. Of note, the SAP Version 1.0 (25 October 2018) was amended after database lock and unblinding, when it was learned that the randomization had not occurred according to the original randomization plan (see section 3.4.2). Considering the error, some patients received the same treatment during two periods. For this reason, the SAP and mock TFLs have been modified in order to properly consider these cases in the statistical analyses, to summarize the data transparently (e.g., showing also the number of treatment periods included in each analysis) and to add additional sensitivity analyses in order to evaluate the impact of patients receiving the same treatment in more than one period. The relevant changes from Version 1.0 of the SAP are described in section 3.8 and will be reported in the Clinical Study Report (CSR).Study Objectives.

The primary objective of this clinical trial is

- *To evaluate the efficacy of CHF 1531 pMDI by comparison with placebo in terms of acute bronchodilator effect (change from baseline in FEV1 $AUC_{0\text{-}12h}$ normalized by time at Day 14).*

There are 2 secondary objectives:

- *To evaluate the effect of CHF 1531 pMDI on other lung function parameters and clinical outcome measures.*
- *To assess the safety and the tolerability of the study treatments.*

3.1 Study Design

The study is a Phase II multi-center, randomized, double-blind, placebo and active-controlled, incomplete block, cross-over, dose ranging study. Randomized subjects will receive four of the six following Study Treatments

- Treatment A*: FF 6µg Total Daily Dose (FF 3µg per inhalation, 1 inhalation bid)
- Treatment B*: FF 12µg Total Daily Dose (FF 6µg per inhalation, 1 inhalation bid)
- Treatment C: FF 24µg Total Daily Dose (FF 6µg per inhalation, 2 inhalations bid)
- Treatment D: FF 48µg Total Daily Dose (FF 12µg per inhalation, 2 inhalations bid)
- Treatment E: Matched placebo for CHF 1531 pMDI (2 inhalations bid)*
- Treatment F**: PERFOROMIST® (formoterol fumarate) Inhalation Solution, 40µg Total Daily Dose (FF 20µg/2mL, 1 unit-dose vial bid administered by nebulization).

*An adequate number of inhalations from Placebo inhalers will be performed to maintain a double blind design.
** Open label.

Background Medication for the Run-in and Treatment Periods

Standardized Background ICS therapy – Open label:

QVAR® 40µg (HFA beclomethasone dipropionate, 40µg), Inhalation Aerosol. Each canister contains 120 actuations.
OR:
QVAR® 80µg (HFA beclomethasone dipropionate, 80µg), Inhalation Aerosol. Each canister contains 120 actuations.

Both dose strengths of QVAR® will be provided by the study sponsor to be dispensed as prescribed by the investigator. The subjects will be prescribed a daily dose of (QVAR® 40 or 80µg/actuation; 1-2 puffs bid) between 80 – 320µg/day, equipotent to their previous ICS (ref. inclusion criterion #6) and this treatment regimen should remain stable for the entire study period. The subject will be asked to not use any other ICS throughout the study.

3.2 Study Schedule

	Pre-screening	Screening	Period 1		Period 2		Period 3		Period 4		F/up Cal	ET
			D 1	D 14	D 1	D 14	D 1	D 14	D 1	D 14		
Visit	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	
Time (weeks)		- 2	0	2	4	6	8	10	12	14	15	Early Terminatio
Time window (days)	-	± 2	-	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	
Informed Consent Form	✓											
Demographic data	✓											
IRT visit confirmation call	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Inclusion / exclusion criteria		✓										
Asthma Action Plan Review		✓	✓	✓	✓	✓	✓	✓	✓			
Eligibility recheck[h]			✓									
Medical history/Previous medication		✓										
Weight and Height		✓										
Physical Examination		✓								✓		✓
Assessment for Oral		✓	✓							✓		✓
Hematology and Blood Chemistry		✓								✓		✓
Serum pregnancy test[a]		✓								✓		✓
Urinary pregnancy test[a]		✓	✓	✓	✓	✓	✓	✓	✓			
12-lead ECG[b]		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Vital signs (DBP/SBP)[b]		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Training on the use of pMDI, diary, PEF, PERFOROMIST®[i]		✓	✓		✓		✓		✓			
Randomization			✓									
Spirometry pre and post-BD[c]		✓										
Pre-dose spirometry[d]			✓	✓	✓	✓	✓	✓	✓	✓		✓
Post-dose 12h serial spirometry			✓	✓	✓	✓	✓	✓	✓	✓		
Pre and post-dose Serum Potassium &			✓	✓	✓	✓	✓	✓	✓	✓		
ACQ questionnaire		✓	✓									
Concomitant medications		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Events assessment		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Rescue Medication		✓										
Dispensation / Return of background ICS:		D	D/R		D/R		D/R		D/R	R		R
Study drug dispensation / return and Accountability			D	R	D	R	D	R	D	R		R
Subject diary/PEF dispensation (D) /return (R)		D	D/R	D/R	D/R	D/R	D/R	D/R	D/R	R		R
Schedule next appointment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓

a In women of childbearing potential only
b At V1 before administration of QVAR®; and at V2-V9: before study-drug dosing and at 30min, 1h, 4h, 8h and 12h post-dose.
c Spirometry will be carried out before and within 30 minutes after the inhalation of 4 puffs of albuterol.
d Pre-dose FEV1, FVC: T -45'and T -15' before administration of study drug at V2-V9 and ET.
e Post-dose serial spirometry (FEV1, FVC): 15', 30', 45', 1h, 2h, 3h, 4h, 6h, 8h, 10h, 11.5h, 12h (V2-V9).
f Serum potassium and glucose: Pre-dose before administration of study drug at V2-V9; and Post-dose at 1.5h, 3h, 5h, 7h, and 11h at V2-V9.
g One commercial albuterol HFA pMDI (200 actuations) will be prescribed and supplied by the investigator to each subject at V1,and resupplied as needed at V2-8 based on assessment of doses used between visits.
h Only Inclusion criteria #3, 4 and Exclusion criteria #1, 3, 8, 9, 13, 14.
i Training on pMDI use will occur on V1 and V2. Training on PERFOROMIST® use will occur when a subject is scheduled to receive Study Treatment F.

3.3 Randomization

3.3.1 Planned Randomization

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).

The Investigator, or designee, at the sites will call the IRT system to screen, randomize subjects and assign treatment kits according to the sequence described in the randomization list. The randomization list will be prepared by a specialized external provider and the whole study team, the investigators and the subjects will be blind to sequence assignment. Subjects will be randomized to one of the 12 possible treatment sequences, according to a balanced incomplete block randomization scheme. For further details refer to Randomization Plan (version 1.0 from 04 JUL 2017). Each randomized sequence will be identified with a number from 1 to 12 until unblinding will be completed. Then the treatment sequence actually randomized (eg.. ABCD) will be used instead of numbers for the analysis.

3.3.2 Randomization Error

An error occurred during a system update to the randomization system on [redacted]. Of note, the randomization files were in 2 parts. Both files were blinded to the study team:

1. Randomization List – This is a list of the treatment sequences, with the 6 treatments coded as 1-2-3-4-5-6. There is one record for each randomization number.
2. Decode List – This is a list which assigns a treatment to each of the codes. There are 6 records, one record for each treatment.

The update which was required was related to shipping and was not intended to have any impact to the randomization. During planning for the system update, the system update was tested in a Test Environment using a dummy Randomization List and a dummy Decode List. The Randomization List was not changed during the update – in either the Test or Production environment. The Decode List was contained within a table that also contained shipping information (referred to as "CTM Types Table"). The CTM Types table was updated to change shipping specifications (no changes to randomization were made). The update was originally made in the Test Environment, which contained the dummy Decode List. The updated CTM types table was then copied from the Test Environment to the Production Environment. After the copy from Test to Production, the dummy Decode List should have been replaced with the actual Decode List. However, this step was erroneously missed, and the dummy Decode List remained within the production environment after the update was completed. After the system update, patients received kits according to the original Randomization List and the dummy Decode List. Patients who were ongoing in the study on [redacted] may have received the same treatment during more than one period.

The update was made relatively early in the study, such that no patient received treatment assignments for all 4 periods prior to the update. For patients who were ongoing in the study at the time of the update, there was a potential to receive the same treatment twice, since these patients received some treatment assignments (those assigned prior to the update) according the original planned Decode List and also some treatment assignments (those assigned after the update) according to the Dummy Decode List.

3.4 Sample Size Calculation

The sample size has been calculated to evaluate the superiority of CHF 1531 pMDI at different doses over placebo in terms of change from baseline in FEV_1 AUC_{0-12h} normalized by time at Day 14. The calculation is based on simulations.

A total of 51 evaluable subjects will provide 96% power to detect a mean difference of 200 mL between each dose of CHF 1531 pMDI and placebo at a two-sided significance level of 0.0125, assuming a within-subject standard deviation of 180 mL. Since four dose levels will be tested, the Edwards and Berry method will be used to control the family-wise Type I error rate at the 0.05 (two-sided) level. In the sample size calculation, the Bonferroni adjustment of the significance level has been taken into account (0.0125 = 0.05/4). This will ensure the required power for each test, since the Edwards and Berry method is uniformly more powerful than the Bonferroni procedure.

Considering a non-evaluable rate of 15%, a total of approximately 60 subjects (5 subjects for each of the 12 treatment sequences) will be randomized.

3.5 Efficacy and Safety Variables

Primary Efficacy Variable

Change from baseline in FEV_1 AUC_{0-12h} normalized by time at Day 14.

Secondary Efficacy Variables

The protocol defines 10 unique secondary efficacy variables but groups them into 3 bullet points in Section 12.3.5 of the protocol and 6 bullet points in Section 8. The variable numbering below is not meant to reflect a hierarchical ordering. Rather, the numbering is meant to allow the listing of all 10 unique secondary efficacy variables but provide the traceability back to the 3 bullet points as outlined in the protocol:

- 1a: Change from baseline in FEV_1 AUC_{0-12h} normalized by time at Day 1.
- 1b: Change from baseline in FEV_1 AUC_{0-4h} normalized by time at Day 1 and Day 14
- 1c: Change from baseline in FEV_1 $peak_{0-4h}$ at Day 1 and Day 14.
- 1d: Change from baseline in pre-dose morning FEV_1 (average of pre-dose FEV_1 measurements) at Day 14.
- 2a: Change from baseline in FVC AUC_{0-12h} normalized by time at Day 1 and at Day 14.
- 2b: Change from baseline in FVC AUC_{0-4h} normalized by time at Day 1 and at Day 14.
- 2c: Change from baseline in FVC $peak_{0-4h}$ at Day 1 and at Day 14.
- 2d: Change from baseline in pre-dose morning FVC (average of pre-dose FVC measurements) at Day 14.
- 3: Time to onset of action (change from baseline in post-dose $FEV_1 \geq 12\%$ and ≥ 200mL) at Day 1.

Safety Assessments

The list of safety assessments presented below is from Section 9 of the protocol. Additional details regarding the safety variables collected during this clinical trial are presented in Section 12.3.6 of the protocol.

- *Adverse Events (AEs) and Adverse Drug Reactions (ADRs)*
- *Vital signs (systolic and diastolic blood pressure)*
- *12-lead ECG parameters (HR, QTcF, QRS, PR)*
- *HR AUC_{0-4h} normalized by time and HR $peak_{0-4h}$*
- *Serum potassium and blood glucose*

3.6 Interim Analyses

No interim analyses are planned for this clinical investigation.

3.7 Changes in the Conduct of Study or Planned Analysis compared to the Study Protocol

The original study design expected that each randomized subject received four of the six Study Treatments. Not in accordance to the Study Protocol, some randomized subjects received the same treatment twice due to the error occurred during the randomization process (see section 3.4.2). The originally planned analyses has been updated in this document to properly handle the cases of patients receiving a treatment during more than one period, which was not foreseen until after database lock and unblinding when the error was identified. Specifically, updates have been made in order to summarize clearly both the number of patients and the number of periods which are included in each analysis. Sensitivity analyses have also been added in order to verify the results of the primary efficacy analysis, which has not been altered. The SAP version 2.0 it is based on the same statistical models as specified in SAP version 1.0, ensuring consistency with the pre-specified analysis models.

3.8 Changes in SAP version 2.0 compared to SAP version 1.0.

All the updates implemented in this version of the SAP, compared to the Final SAP version1.0, are listed in the following table. For each modified section, a summary of the change is reported.

Section	**SAP version 2.0**
3 Protocol / Clinical Investigation Plan	Added text to describe why an Amendment to SAP 1.0 was needed.
3.4 Randomization	"Section 3.4 Randomization" became "3.4.1 Planned Randomization". Added section "3.4.2 Randomization Error" where the error occurred during the randomization process is described in details.

3.8 Changes in the Conduct of Study or Planned Analysis compared to the Study Protocol	Updated the text to describe why an amendment to the SAP 1.0 was needed. Added section "3.8.1 Changes in SAP version 2.0 compared to SAP version 1.0" where the list of all changes is reported.
6.1 Analysis Populations	Added text to specify that sensitivity analysis (added with SAP version 2.0) will be performed on the ITT population.
6.2 Treatment Misallocation	Added text to state that the treatment sequence assigned by the randomization system will be used in the statistical analysis instead of the one originally planned. Furthermore, inconsistency between the originally planned randomization and the actual implemented randomization has not be considered as a reason for exclusion from any analysis.
8.1 General Methods	General methods for continuous and categorical variable moved in the new section "8.1.1 Rules for Patients Receiving the Same Treatment in Two Periods". General Methods to handle patients receiving the same treatments in more than one period have been added for both continuous and categorical variables.
8.2 Specific Methods for Efficacy Analyses- Analyses Based on Mixed Models	The way to handle patients receiving the same treatment in multiple periods in the analysis based on mixed models (primary and secondary efficacy endpoints) has been added to this section with an example. The model has not been modified. Three sensitivity analyses have been added.
8.2 Specific Methods for Efficacy Analyses- Analyses Based on the Time to Onset	The way to handle patients receiving the same treatment in multiple periods in the analysis based on Time to Onset has been added to this section with an example.
8.3 Specific Methods for Safety Analyses	The way to handle patients receiving the same treatment in multiple periods has been added to this section.
10 Overview of Tables, Listings and Figures	The text has been updated to specify that no table will be presented by sequence, listings including sequences will report sequences as assigned by the randomization system and all listings will be sorted by patient ID.

10.1 Dispositions of subjects	The disposition summary table originally planned to be reported by treatment sequence, will be reported overall only. The disposition summary table originally planned to be reported by study treatment will be presented on a period-level, counting each treatment period once and including the number of periods as the denominator. The randomization schedule listing will be updated to show the original intended randomization schedule and how it differs from the randomization which was actually implemented by the randomization system and the treatments administered.
10.2 Protocol Deviations	The summary of Major Protocol Deviations has been updated to include patients receiving a treatment twice. The summary will be based on a per-period level and patients receiving a treatment twice will be considered twice in the corresponding treatment column.
10.3 Analysis Sets	The summary of analysis sets will include also the number of patients in each population, regardless of the number of periods (counted only once) and the total number of periods in each population. Percentages will be based on the total number of periods.
10.4.1 Demographic Characteristics, Asthma History, and Smoking Habits	The summaries of Demographic Characteristics, Asthma History, and Smoking Habits, originally planned to be reported by treatment sequence, will be reported overall only.
10.4.2 Medical History	The summary of Medical History, originally planned to be reported by treatment sequence, will be reported overall only.
10.4.3 Baseline Subject Characteristics	The summaries of Baseline Subject Characteristics (Central spirometry and reversibility test, ECG results at Visit 1, Vital signs at Visits 1 and 2, ACQ score at Visits 1 and 2) originally planned to be reported by treatment sequence, will be reported overall only.
10.4.4 Previous, Maintained and Concomitant Medications	Previous medication summary, originally planned to be reported by treatment sequence, will be reported overall only. Summaries of Maintained and Concomitant Medication have been updated to include patients receiving a treatment twice and they will be based on a per-period level; patients receiving a treatment twice will be considered twice in the corresponding treatment column.
10.5.1 Background ICS medication	Previous asthma treatment summary and summary of background medication exposure and compliance during run-in, originally planned to be reported by treatment sequence, will be reported overall only. Summaries of background medication exposure and compliance during treatment periods and washout periods have been updated to include patients receiving a treatment twice and they will be based on a per-period level; patients receiving a treatment twice will be considered twice in the corresponding treatment column.

10.5.2 Study drug	Summary of treatment exposure and compliance during the treatment periods has been updated to include patients receiving a treatment twice. Summary will be based on a per-period level and patients receiving a treatment twice will be considered twice in the corresponding treatment column.
10.5.3 Compliance with the use of Diary	Summary of compliance with the use of diary in run-in period, originally planned to be reported by treatment sequence, will be reported overall only. Compliance with the use of Diary in treatment and Washout periods summaries have been updated to include patients receiving a treatment twice. Summaries will be based on a per-period level and patients receiving a treatment twice will be considered twice in the corresponding treatment column.
10.6.1 Primary efficacy variable	Primary efficacy variable summary has been updated to include patients receiving a treatment twice. For patients receiving the same treatment in 2 periods, the 2 available data points will be averaged prior to calculation of the summary statistics for all subjects. The number of treatment periods considered will be added to the table. The same approach has been described also for the summary of FEV1 at each time point. The primary efficacy analysis has not been modified. A reference to the three sensitivity analyses defined in section 8.2 has been added.
10.6.2 Secondary efficacy variables	Summaries of secondary efficacy variables have been updated to include patients receiving a treatment twice. For patients receiving the same treatment in 2 periods, the 2 available data points will be averaged prior to calculation of the summary statistics for all subjects. The number of treatment periods considered will be added to the tables. The same approach has been described also for the summary of FVC at each time point.
10.7.1 Adverse Events	Summaries of TEAEs have been updated to include patients receiving a treatment twice. They will be considered twice in the corresponding treatment group. The number of subjects ("n"), the number of treatment periods ("n periods") and the number of events will be presented. The percentages will be based on the number of treatments periods in each group.
10.7.2 Vital Signs	Summary of vital signs has been updated to include patients receiving a treatment twice. For patients receiving the same treatment in 2 periods, the 2 available data points will be averaged prior to calculation of the summary statistics for all subjects. The number of treatment periods considered will be added to the table.

10.7.3 ECGs	Summary of continuous ECGs parameters has been updated to include patients receiving a treatment twice. For patients receiving the same treatment in 2 periods, the 2 available data points will be averaged prior to calculation of the summary statistics for all subjects. The number of treatment periods considered will be added to the table. Summary of QTcF values has also been updated such that patients receiving a treatment twice will contribute only once to the summary statistics, using the highest observed QTcF value.
10.7.4 Clinical Laboratory Evaluation	Summary of Clinical Laboratory data has been updated to include patients receiving a treatment twice. For patients receiving the same treatment in 2 periods, the 2 available data points will be averaged prior to calculation of the summary statistics for all subjects. The number of treatment periods considered will be added to the table.

4 General Definitions

4.1 Report Language

The output of the analyses will be prepared in (USA) English.

4.2 Analysis Software

The statistical analysis will be performed using the SAS® statistical software package (Version 9.3).

5 Data Preparation

5.1 Data Handling and Medical Coding

5.1.1 Data Handling

For data quality control, please refer to the Data Management Plan (Version 1.0 from 03 AUG 2017) including the Data Validation Plan (Version 2.0 from 04 AUG 2017).

5.1.2 Coding

The following dictionaries will be used for coding in the analysis:

Medical History, Concomitant Diseases, Surgeries and Procedures

Medical Dictionary for Regulatory Activities (MedDRA) coding system, version 20.0.

Prior and Concomitant Medications

World Health Organization Drug Dictionary (WHO-DD) version January 2017.

Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) coding system, version 20.0.

5.2 CDISC

All output as defined in the SAP will be generated based on CDISC ADaM datasets. Specifications for the ADaM datasets (as well as SDTM datasets) are described in a separate document.

5.3 SAS-Programming Quality Level

The following quality level of programming deliverables will be applied:

All statistical output will receive a tailored Quality Control (QC) approach by:

- Full independently double programmed reproduction (QC) of results of
  - CDISC ADaM datasets
  - Unique Tables and Graphs
  - All tables and figures reporting inferential analyses results
- Listings will not be double programmed. The programming to generate the listings will be reviewed in accordance with the [redacted] procedure for all SAS programs.
- All tables, listings and graphs will undergo comparison with specifications (i.e. SAP and templates), cross checking with other tables, listings and graphs, the individual logs from the SAS programs will be reviewed to ensure all errors, warnings, and uninitialized variable messages have been rectified.
- A Senior Review will also be performed by a reviewer independent of the study team. The reviewer studies all tables, listings and graphs for consistency and correctness, and pre-empts customer comments. This allows points of interest to be highlighted and discussed at customer hand-over.

All SDTM datasets, ADaM datasets, and tables, listings, and figures will be QC'ed by independent programmers, the study biostatistician, and a senior review as per the [redacted] SOP (SOP-ST-04) SAS Programming, Validation, and QC version 3.0.

5.4 Data from third parties

Data provided by third parties, not contained in the clinical database, will be included in the SAS data repository. Paper diary will contain drug intake details, PEF values, rescue medication and Asthma Symptom Score. Diary data will be databased.

These third parties are:

- [redacted]: central laboratory data.
- [redacted]: ECG data, spirometry data.
- [redacted]: supplies the randomization schedule to [redacted]
- [redacted]: randomization data from the IRT system.

6 Analysis Populations and Subgroups

6.1 Analysis Populations

- ***All Enrolled Subjects:***
- ***All Randomized subjects***
- ***Safety population:*** *all randomized subjects who receive at least one dose of study drug.*
- ***Intention-to-Treat population (ITT):*** *all randomized subjects who receive at least one dose of the study drug and with at least one available evaluation of efficacy (primary or secondary efficacy variables) after the baseline.*
- ***Per-protocol population (PP):*** *all subjects from the ITT population without any major protocol deviation (i.e., wrong inclusions, poor compliance and 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.*

The inclusion in the Safety, in the ITT and in the PP population will be defined on a per-period basis.

Since the superiority of CHF 5259 pMDI at different doses over placebo will be tested, the primary efficacy analysis and the associated sensitivity analyses will be based on the ITT population. The primary efficacy analysis will be also performed on the PP population for sensitivity purposes. The secondary efficacy variables will be analyzed in the ITT population. The safety variables will be analyzed in the Safety population.

All 3 populations (Safety, ITT, and PP) will be used for the presentation of demographics, Asthma history, Pre-Study Smoking Habits, spirometry and reversibility.

The medical history/concomitant diseases, and exposure/compliance to study drug results will be presented using the ITT and Safety populations.

Medications, ACQ score, compliance with use of the diary, exposure/compliance to background medication, and protocol deviations will be reported using the ITT population.

6.2 Treatment Misallocation

The majority of the subjects did not receive treatment assignments according to the originally planned treatment sequence. The randomization system erroneously assigned different treatments from to the originally planned ones (See section 3.4.2). For purposes of statistical analysis, ‘as randomized’ is considered to mean “as allocated by the randomization system”. While this differs from the original intended randomization plan, it accurately reflects the randomization which has occurred and therefore provides the most meaningful study results.

Accordingly, the inconsistency observed between the originally planned randomization and the actual implemented randomization is not considered as a reason for exclusion from any analysis, as long as the treatment received corresponded to the treatment allocated by the

randomization system. Of note, one patient who received a treatment other than the one assigned by the randomization system (as documented in the DRR version 1.0, 26 October 2018) will be considered as having received the wrong treatment.

In case of deviation between the as-randomized (i.e., as allocated by the randomization system) treatments and the treatments actually received, the treatments actually received will be used in the safety analyses (i.e. an as-treated analysis will be performed). The following rules will be applied in the construct of the populations:

- Subjects randomized but not treated will be excluded from the Safety, ITT, and PP populations.
- Subjects treated but not randomized will be excluded from the ITT and PP population, given there will be no randomized treatment. These subjects will be summarized based on the treatments they received and will be counted in the Safety population.
- Subjects who were randomized, but took the incorrect study drug (i.e. study drug other than what was allocated by the randomization system) for the duration of one or more periods, will be summarized based on their assigned treatment for those periods for the ITT population and excluded from the PP population. These subjects will be summarized based on the treatments that they received for the safety analyses.
- Subjects who were randomized, but took the incorrect study drug(i.e. study drug other than what was allocated by the randomization system) for part of a period (e.g. the subject began the period by taking the incorrect study drug at Day 1 but switched to correct study drug before Day 14) will be discussed during the Blind Data Review Meeting, and the decisions will be agreed prior to unblinding, and documented in the Data Review Report prior to unblinding.

6.3 Subgroup Definitions

There are no specific subgroups that are planned for analysis.

7 Definition of Time Points and Analysis Variables

7.1 Definition of Time Points

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

Period Definition

Periods used in the analysis of this study are defined as below:

- Run-in Period: Morning of Visit 1 through the evening of the day before Visit 2.
- Treatment Period 1: from the morning of Visit 2 to the morning of Visit 3
- Treatment Period 2: from the morning of Visit 4 to the morning of Visit 5
- Treatment Period 3: from the morning of Visit 6 to the morning of Visit 7.
- Treatment Period 4: from the morning of Visit 8 to the morning of Visit 9.

Between each two consecutive treatment periods there is a Washout period, for a total of three Washout periods.

Visits labels are assigned according to the eCRF visits as follow:

eCRF Visit labels	Study Period	TLFs Visit labels
Visit 1	Run-in	Visit 1
Visit 2	Treatment Period 1	Period 1 Day 1
Visit 3		Period 1 Day 14
Visit 4	Treatment Period 2	Period 2 Day 1
Visit 5		Period 2 Day 14
Visit 6	Treatment Period 3	Period 3 Day 1
Visit 7		Period 3 Day 14
Visit 8	Treatment Period 4	Period 4 Day 1
Visit 9		Period 4 Day 14
Visit 10	Follow-up	Visit 10

Start/End of the Randomized Treatment Period (Study Level)

Since many algorithms used in the statistical analyses require the start and/or the end of the randomized treatment periods to be identified, ad-hoc variables specifying these dates will be defined. Four treatment periods are defined. The date of start/end of the randomized treatment period will be set according to the following rule:

- The date of **Start of the Randomized Treatment Period (Study Level)** should coincide with the date of Visit 2, the randomization date and the date of first randomized study drug intake. However, discrepancies between these dates may arise and the most appropriate date to be used in such situations requires a case-by-case evaluation. The

date of the start of the randomized treatment period will be initially set equal to the date of first randomized study drug intake for all subjects. The need for deviations from this rule in single cases will be evaluated during the data review and documented in the Data Review Report. As a consequence, the distinction between diary data from the run-in and the treatment period will not be based on the EPOCH variable included in the SDTM datasets, but on the algorithms defined in the SAP.

- If Visit 9 or Early Termination visit was completed, then the date of **End of the Randomized Treatment Period (Study Level)** will be defined as the date of Visit 9/Early Termination. Otherwise, the date of End of Randomized Treatment Period will be defined as the maximum of [Date of Last Study Drug Intake, date of last clinic visit (excluding follow up phone call and any unscheduled visits after the last dose)].

Period durations (days)

Treatment period duration is defined for each period using the following rule:

- Treatment Period *x*: Date of Day 14 Visit – Date of Day 1 Visit + 1, per period.

Between each two consecutive periods there is a Washout period. The duration of each Washout period is defined as:

- Washout Period *x*: ((Date of the Day 1 visit of next period(*x*+1) -1) minus Date of Day 14 visit of current period *x*) +1.

For treatment period duration and washout period duration, if the period was started but not completed, then the end of period date will be replaced with the date of End of Randomized Treatment Period.

The duration of the Run-in Period is:

- Run-in Period: (Date of Visit 2 -1) – Date of Visit 1 +1

Date of first/last study drug intake per period

Date of first study drug intake in each period is derived as the minimum of 'Date/Time of administration' between the 2 inhalations (puffs) of the Morning Dose collected on the 'Study drug administration at the clinic' eCRF page of Visit 2 for Period 1, Visit 4 for Period 2, Visit 6 for Period 3, Visit 8 for Period 4. While subjects randomized to open-label PERFOROMIST® will receive a continuous nebulized treatment over approximately 10 minutes, the Date of first study drug intake for subjects treated with PERFOROMIST® coincide with the start 'Date/Time of administration' of the Morning Dose collected on the 'Study drug administration at the clinic' eCRF page.

Note: The date and time of drug administration at each visit are mandatory variables to be reported in the CRF; no missing or partial data can be accepted. Only eCRF data will be considered for the date of first study drug intake.

Date of last study drug intake in each period is derived as the maximum of 'Date/Time of administration' between the inhalations (puffs) collected on the 'Study drug administration at

the clinic' eCRF page of Visit 3 for Period 1, Visit 5 for Period 2, Visit 7 for Period 3, Visit 9 for Period 4. If the date of the last intake of study drug at Day 14 in a period is missing or partially missing, but the date of at least one dose of the study drug is recorded in the diaries, the date of the last study drug intake in that period will be imputed using the following rule:

max [date of study drug intake in the diaries per period]

If a period is the last period in which the subject was treated then the date of last dose of that period will be set equal to the 'Date of last intake of study drug' on the 'Study Termination' eCRF page. If the date of last intake of study drug is missing or partially missing, but the date of at least one dose of the study drug is recorded in the diaries or at the clinic, the date of the last randomized study drug intake will be imputed using the following rule:

max [date of last study drug intake in the diaries, date of last study drug intake at the clinic visits]The need for deviations from these rules in single cases will be evaluated during the data review and documented in the Data Review Report.

Time to discontinuation from the study

Time to discontinuation will be calculated for all randomized subjects, including subjects who complete the study. For subjects randomized but not treated, the time to discontinuation from the study will be imputed as 0. Subject disposition data will be collected on the 'Study Termination form' eCRF page, which provides information about study completion status of a subject. Study discontinuation is recorded along with the main reason for withdrawal. The primary reason for discontinuation could be early withdrawal or lost to follow up. Patients completing the study will be censored at the Date of Completion. Patients lost to follow up will be considered as having an event at the date of Discontinuation recorded on the 'Study Termination" eCRF page.

The time to completion/discontinuation from the study (weeks) is defined as:

(date of completion/discontinuation - date of start of randomized Treatment Period 1) / 7

Baseline definitions

For FEV1 and FVC, the baseline value for each period is defined as the average of the pre-dose measurements on Day 1 (45 min and 15 min pre-dose) of the treatment period. If only a single value is recorded for FEV1 or FVC, the value will be used as the baseline value. If no measurement is available, then the pre-dose value will be considered as missing (for FEV1, FVC) for that treatment period.

For safety variables the baseline for each period is defined as pre-dose measurements on Day 1 of each treatment period.

For laboratory parameters the baseline values are the ones collected at Visit 1.

7.2 Baseline and Derived Analysis Variables

The purpose of this section is to describe the calculation of all derived variables. All other variables that are obtained directly from the eCRF system with no derivation are not described in this section.

7.2.1 Demographic Characteristics

- Age of the subject will be calculated by the IVRS system based on the date of birth and date of Pre-Screening Visit (Visit 0) entered into the system.

7.2.2 Asthma History and Pre-Study Smoking Habits

- The time since first Asthma diagnosis (months) will be calculated as the (Visit 1 date minus the date of first diagnosis)/30.4375.
- Age at First Asthma Diagnosis (years) will be calculated in SAS using the following formula: floor(yrdif(date of birth, date of first diagnosis, 'AGE')).
- The Duration of Smoking (years) will be calculated using the start/stop date of smoking (smoking stop date - smoking start date + 1)/365.25).
- The number of pack at year will be calculated within the eCRF

Only the month and the year (not the day) is recorded on the eCRF for Date of first diagnosis and smoking start/stop date. The first day of the month will be assumed for these dates in order to calculate time duration variables.

In order to calculate the duration, the following rules will be applied for the partial dates: if the month is missing, January 1st will be assumed. When the start date is completely missing, the time duration variable will not be calculated.

7.2.3 Baseline Subject Characteristics

- Asthma Control Questionnaire (ACQ) at Visit 1, Visit 1.1 and Visit 2 will be calculated within the eCRF. If Asthma Control Questionnaire (ACQ) is repeated in a in a (pre-randomization) rescheduled visit (called Visit 1.1 in the eCRF) then the ACQ calculated at Visit 1.1 will be used for the analysis.
- Medical/Surgical History and Concomitant Diseases will be collected during Visit 1. All conditions that are not indicated as ongoing will be considered as medical/surgical history, while conditions indicated as ongoing will be considered as concomitant diseases.
- Body Mass Index (kg/m^2) is calculated as Weight (kg) / [Height (m)]^2.

7.2.4 Spirometry Performed at Screening

Spirometry (FEV_1 and FVC) will be carried out before bronchodilator and within 30 minutes after intake of 4 puffs of albuterol HFA (90 µg/ actuation) at Visit 1 (screening). The reversibility parameters (ΔFEV_1 (mL) and % ΔFEV_1) will be calculated in the eCRF.

If the reversibility test or any other screening assessments of Visit 1 are repeated in a (pre-randomization) rescheduled visit (called Visit 1.1 in the eCRF), then all values of the rescheduled visit will be used for the analysis.

7.2.5 Medications

Medications will be split into four categories:

- **Previous medications** are those medications started and stopped prior to the initial exposure to the study drug (medication start date < date of first study drug intake of Period 1and medication stop date ≤ date of first study drug intake of Period 1).
- **Concomitant medications** are all medications started during the treatment period (date of first study drug intake of Period 1< medication start date < date of last study drug intake of last period attended, with the exception of medications taken only during Washout - see the definition below).
- **Medications taken only during washout** are all medications started after the end of one randomized period and stopped before the start of the following randomized period. (For at least one treatment Period x (Period 1, Period 2, Period 3): medication start date > date of last study drug intake in Period x and medication stop date < date of first study drug intake in Period x+1)
- **Maintained medications** are all medications started before initial exposure to the study drug and ongoing at initial exposure to the study drug (medication start date < date of first study drug intake of Period 1and medication stop date > date of first study drug intake of Period 1).
- **Post-treatment medications** are all medications started on or after the last dose of study drug (medication start date ≥date of last study drug intake of last period attended)

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 performed according to the available parts of the start and the stop dates. The medications will be allocated to the first category allowed by the available data, according to the following order:

1. concomitant medication;
2. maintained medication;
3. Medications taken only during washout
4. post-treatment medication;
5. previous medication.

Information on concomitant medications is retrieved from the 'Concomitant medications' eCRF page.

7.2.6 Concomitant Medications and Treatment Assignment

The following rules are applied for assigning medications to a specific study treatment group:

- Previous medications will not be assigned to study treatment groups since they will be summarized by sequence.

- Concomitant medications and maintained medications will be assigned to the study treatment(s) received by the patient whilst using the concomitant medication, by comparing the start and stop date of the concomitant medication with the start and stop dates of each study treatment. A concomitant/maintained medication could be assigned to more than one study treatment group.
- Medications taken only during washout and post-treatment medications will be assigned to the last study treatment received prior to the Washout period or study completion/discontinuation.

Where a medication start and/or stop date is fully or partially missing, so that it's unclear as to which study treatment the medication is associated, the medication will be assigned to both treatments.

7.2.7 Concomitant Procedures

Procedures will be split into three categories:

- **Previous procedures:** are all procedures started and stopped prior to the initial exposure to the study drug (procedures start date < date of first study drug intake of Period 1 and procedures stop date ≤ date of first study drug intake of Period 1)
- **Maintained procedures** are all procedures started before initial exposure to the study drug and ongoing at initial exposure to the study drug (procedures start date < date of first study drug intake of Period 1 and procedures stop date > date of date of first study drug intake of Period 1).
- **Concomitant procedures** are all procedures started during the treatment period (date of first study drug intake of Period 1 ≤ procedures start date < date of last study drug intake of last period attended), with the exception of procedures received only during Washout (see the definition below).
- **Procedures performed only during Washout** are all procedures started after the end of one randomized treatment period and before the start of the following randomized treatment period. (For at least one treatment Period x (Period 1, Period 2, Period 3): procedure start date > date of last study drug intake in Period x and procedure stop date < date of first study drug intake in Period x+1)
- **Post-treatment procedures** are all procedures started on or after the last dose of study drug (procedures start date >= date of last dose of study drug of last period attended)

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

1. concomitant procedures;
2. procedures taken only during washout
3. post-treatment procedures
4. maintained procedures
5. previous procedures.

Information on concomitant procedures is retrieved from the 'Concomitant procedures' eCRF page. Procedures will be listed only.

Assignment of procedures to a study treatment group follows the same rules as stated in section 7.2.6.

7.2.8 Treatment Exposure and Compliance – Background ICS Medication

The approach below defined for the calculation of compliance assumes no intake of the background medication in case of missing data.

In each period a Diary Card is provided. It should be completed by the patients from the evening of Visit 1 to the morning of Visit 2 for Run-in period, from the evening of Day 1 to the morning of Day 14 for Treatment periods and from the evening of Day 14 to the morning of the following visit for Washout periods. In each period, all data recorded outside the pre-specified intervals will not be considered for the calculation of compliance.

Run-In Period / Exposure and Compliance

Background ICS medication (QVAR®) is prescribed to subjects during the Run-in Period. The Run-In Period starts at Visit 1 and runs through the day before Day 1 of Treatment Period 1. Exposure during the Run-in Period is based on actual dosing date/times and not visit dates.

Exposure will be calculated as the date of last dose of the Run-in Period – date of first dose of the Run-in Period + 1 day.

Compliance with background ICS medication during the Run-in Period is based on eCRF and diary data. If, on a visit day, information is available from both eCRF and diaries, data entered by the investigator in the eCRF will be taken into account.

The evaluation of compliance will be based on the number of puffs following the formula presented below:

$$\frac{\text{Total number of administered puffs (as recorded in the Subject Diary and / or Background Medication Administration eCRF page)}}{\text{Total number of scheduled puffs}} x\ 100\%$$

The total number of **scheduled puffs per day** is the sum of the 'Number of puffs the subject has been instructed to take: Morning puffs' plus 'Evening puffs' as recorded on the Screening 'Background Medication Administration for Asthma' eCRF page.

The total scheduled number of puffs during the Run-in Period is defined as:

Run-in Period duration x [scheduled number of puffs per day]

Treatment Periods / Exposure and Compliance

Compliance to background ICS medication during each Treatment Period should be calculated considering data recorded, from date of start of each randomized treatment period to date of end of each randomized treatment period.

For each Treatment Period, exposure to background ICS medication (days) will be calculated as date of last background ICS medication intake during the treatment period- date of first background ICS medication intake during the treatment period+ 1 day.

Compliance to background ICS medication per Treatment Period is based on eCRF and diary data. If on a visit day information is available from both eCRF and diaries, data entered by the investigator in the eCRF will be taken into account.

The evaluation of compliance will be based on the number of puffs following the formula presented for Run-in Period.

The total scheduled number of puffs during each Treatment Period is defined as:

- For subjects who had their last background ICS medication dose on the last scheduled dosing day of the Treatment Period **[i.e. Day 14]** the scheduled number of puffs = exposure to background ICS medication (days) x [scheduled puffs per day] minus [scheduled evening puffs on the last scheduled dosing day]

- For subjects who had their last background ICS medication dose on any day before the last scheduled dosing day of the Treatment Period **[e.g. an early discontinuation**] the scheduled number of puffs = exposure to background ICS medication (days) x [scheduled puffs per day]

If the date of the last dose of background ICS medication = date of first dose of background ICS medication, the scheduled number of puffs will be 1 day * [scheduled puffs per day].

Washout Periods / Exposure and Compliance

Exposure during each Washout Period are based on actual dosing date/times and not visit dates.

For each Washout Period, exposure will be calculated as the date of last dose of the Washout Period – date of first dose of the Washout Period + 1 day.

The evaluation of compliance will be based on the number of puffs following the formula presented for Run-in Period. The total number of scheduled puffs per day are derived as per Run-in Period.
Compliance during Washout Periods will be evaluated by study treatment group. Compliance to background ICS medication will be assigned to the last study treatment received prior to the Washout Period.

The total scheduled number of puffs during each Washout Periods is defined as:

- Scheduled number of puffs = Washout Period duration x [scheduled puffs per day] minus [scheduled morning puffs on the first scheduled dosing day]. Subjects should receive their first background ICS medication dose of the washout period in the evening on the last dosing day of the Treatment Period **[i.e. Day 14],** so scheduled morning puffs should not be counted in the washout compliance calculation.

Any level of compliance in the interval [65%; 135%] is considered as satisfactory after randomization. Therefore, the following categories will be presented:

- Treatment compliance < 65%
- 65% ≤ Treatment compliance ≤ 135%
- Treatment compliance > 135%.

Compliance with background ICS medication will also be summarized using the following categories for the Run-in Period, Treatment Periods and Washout Periods:

- [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%

Exposure and compliance will be presented for the Run-in Period by sequence and for the Treatment and Washout Periods by study treatment group.

7.2.9 Treatment Exposure and Compliance - Study Drug Administration

The actual date and time of study drug administration will be used to calculate exposure. The following dosing schedule will be followed. Study drugs will be administered twice-a-day (in the morning and in the evening), according to the randomized treatment sequence, except for Day 14 of each Treatment Period (Visit 3, Visit 5, Visit 7, Visit 9) when only the morning dose is administered:

Morning administration (between 8-10 am):

- Study Treatments A – E:
  One puff from the canister numbered 1
  One puff from the canister numbered 2
- Study Treatment F:
  One nebulized treatment of (2mL) vial to be inhaled through standard jet nebulizer

Evening administration (between 8-10 pm):

- Study Treatments A – E:
  One puff from the canister numbered 1
  One puff from the canister numbered 2
- Study Treatment F:
  One nebulized treatment of (2mL) vial to be inhaled through standard jet nebulizer

The first and last dosing occasions for study drug are expected to be taken during the visit dates, however exposure is based on actual dosing date/times and not visit dates. See Section 7.1 for the definition of the study periods and period durations (days).

For the calculation of the number of administered and scheduled puffs, the dosing occasions from the first to the last study drug intake for each period will be taken into account. In each period, all data recorded in subject diaries before Day 1-Evening and after Day 14-Morning will not be considered for the calculation of compliance. Any study drug recorded in the Subject Diary after the Date of last intake of study drug (as recorded on the 'Study Termination' eCRF page) will be ignored for study drug compliance calculations.

If Date of last intake of study drug (as recorded on the 'Study Termination' eCRF page) is missing or partially missing, dosing occasions of the study drug recorded in the diaries or at the clinic will be taken into account for deriving the 'last randomized study drug intake' as defined in Section 7.1.

During each Treatment Period, Treatment exposure will be calculated as the Date of last intake of study drug of the period – date of first intake of study drug of the period + 1 day.

The evaluation of compliance is done using the following formula:

$$\frac{\text{Total number of administered puffs (as recorded in the Subject Diary and / or Study Drug Administrationat the Clinic eCRF page)}}{\text{Total number of scheduled puffs}} \; x\ 100\%$$

The **total number of administered puffs** will be calculated by adding up the number of puffs taken during each Treatment Period, as recorded in the Subject Diary or 'Study Drug Administration at the Clinic' eCRF page.
It should be noted that 2 puffs (for treatment arms A-E) or 1 unit-dose vial nebulization (for Arm F) should be taken twice a day during the Treatment Period (from Day 1 (V2, V4, V6, V8) until the day before V3, V5, V7, V9 respectively) and 2 puffs (for treatment arms A-E) or 1 unit-dose vial nebulization (for Arm F) should be taken once a day in the morning on V3, V5, V7 and V9 [On these end-of-Treatment Period visits, the morning dose occurs in the clinic and there is no evening dose]. The total number of scheduled puffs is defined during each Treatment Period as:

- For subjects who had their last study drug dose on the last scheduled dosing day in the Treatment Period **[i.e. Day 14 of Treatment Period],** the scheduled number of puffs = Treatment exposure (days) x [scheduled puffs per day] minus [scheduled evening puffs]

- For subjects who had their last study drug dose on any day before the last scheduled dosing day in the Treatment Period **[i.e. an early discontinuation**], the scheduled number of puffs = Treatment exposure (days) x [scheduled puffs per day].

- If a subject is randomized into the study and discontinues the same day, then the subject was included in the study for 1 day. Hence, the expected number of puffs would be 1 day * [scheduled puffs per day]

Information on study drug intake is retrieved from the eCRF (on visit days) and subject diaries. If on a visit day information is available from both eCRF and diaries, data entered by the investigator in the eCRF will be taken into account.

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

Any level of compliance in the interval [65%; 135%] is considered as satisfactory after randomization. Therefore, the following categories will be discerned for Study Treatment:

- Treatment compliance < 65%
- 65% ≤ Treatment compliance ≤ 135%
- Treatment compliance > 135%.

The Study Treatment compliance will also be summarized as per following categories:

- [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%

7.2.10 Compliance with the use of Diary

Compliance with the use of Diary is based on visit dates. See Section 7.1 for the definition of the study periods and period durations (days). On a given day, if any questions are answered in the diary (beyond a data, since these are not entered daily), then the diary is considered as used for that day, even if all questions are not completed.

The evaluation of compliance per period, including Run-in, Treatment and Washout Periods, is done using the following formula:

$$\frac{\text{Total number of days in the period with data recorded in the Subject Diary}}{\text{Period duration}} \; x \; 100\%$$

For Run-in and Washout periods, diary is expected to be completed also on the morning of the first day of the following Treatment Period. For this reason 1 day will be added to Run-in and Washout Period durations.

Compliance during Washout periods will be assigned to treatments follow the same rules as for Medications taken only during Washout in paragraph 7.2.7.

The compliance with the use of Diary will be summarized as per following categories:

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

Compliance with the use of Diary will be presented by sequence for the Run-in Period and by study treatment group for the Treatment and Washout Periods.

7.2.11 Efficacy Variables

● Overview

All spirometry results will be graded by an independent reviewer at [redacted]. The grades after the Best Test Review are: U = Unacceptable, A = Acceptable, and B = Borderline Acceptable. All spirometry values, including the values scored with a grade "Unacceptable", will be considered in the statistical analyses. This follows the approach recommended by the paper by Hankinson et al., where it was concluded that quality assessment regarding the acceptability of individual blows should be primarily used as an aid to good quality during testing rather than a reason to subsequently disregard data.

Spirometry data together with the time of scheduled time points are imported from external [redacted] data.

In addition, the spirometry values excluded from the analysis based on the decisions taken during the Blind Data Review Meeting (e.g., due to technical issues) will be considered to be missing prior to the calculation of the derived variables. In the listings, these assessments will be shown and flagged, to highlight their exclusion from the analyses.

● Primary Efficacy Variable

The primary efficacy variable is *the change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 14*. The baseline value is the average of the T-45 and T-15 min pre-dose FEV_1 measurements on Day 1. FEV_1 is a continuous variable derived from spirometry data ([redacted]). FEV_1 $AUC_{0\text{-}12h}$ will be calculated at *Day 14*. AUC normalized by time will be calculated based on the actual times using the linear trapezoidal rule:

$$\left\{\sum_{\mathbf{i}}[(\mathbf{t_i}-\mathbf{t_{i-1}})(\mathbf{FEV1_i}+\mathbf{FEV1_{i-1}})/\mathbf{2}]\right\}/\mathbf{time}$$

where:

for t_0, $FEV1_0$ is the pre-dose average of T -45' and T -15' before study drug administration at Day 14 of each Treatment Period.

t_0 is the actual time of the administration of the first morning dose of study drug,

for i = 15 min, 30 min, 45 min, 1h, 2h, 3h, 4h, 6h, 8h, 10h, 11.5h and 12h, $FEV1_i$ is the actual FEV1 value at each time point and t_i is the actual time of sample i.

time is the actual elapsed time from t_0 until t_{12}.

For the calculation, all valid measurements are taken and, in addition, the following imputation rules apply:

- If one of the spirometry 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 (corresponding to time 0 for the calculation of AUC). If no measurement is available, then the pre-dose value will be considered as missing.
- If the pre-dose value is not available, the entire curve will be considered as missing
- The linear trapezoidal rule will allow $AUC_{0\text{-}12h}$ to be calculated if a single, isolated missing value exists. This is akin to replacing the missing value by linear interpolation using the adjacent values
- If the value at 12h post-dose is missing, it will be replaced by the value at 11h30.
- If two or more consecutive post-dose time points have a missing observation, the entire FEV_1 $AUC_{0\text{-}12h}$ for that day will be missing.
- If in total three or more post-dose time points have missing values, the FEV_1 $AUC_{0\text{-}12h}$ for that day will be missing.
- In case of missing actual time, the theoretical or planned time is used.

If a subject uses rescue medications within the 12-hour post-dose period during which the FEV_1 measurements are obtained at Day 14, then all FEV_1 measurements will be used in the calculation of the FEV_1 $AUC_{0\text{-}12h}$ and analyzed as part of the ITT Population with no exception. In case of rescue medication intake during the serial spirometry (from pre-dose to 12 h post-dose) or during the 6 h washout pre-dose, cases will be reviewed during the DRM and documented in the DRR. As a general rule, all spirometry data recorded from the time of rescue medication intake onwards for 6 hours will be excluded from the analysis of primary efficacy endpoint for the PP population.

Secondary Efficacy Variables

As the secondary efficacy variables will be analyzed in the ITT population, no data will be excluded from the analysis due to the intake of rescue medication during the serial spirometry or the 6 h washout pre-dose.

- 1a: *Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 1*

FEV_1 is a continuous variable derived from spirometry data ([redacted]). FEV_1 $AUC_{0\text{-}12h}$ will be calculated on Day 1. The baseline value is the average of the T-45 and T-15 min pre-dose FEV_1 measurements on Day 1. The calculation of the FEV_1 $AUC_{0\text{-}12h}$ on Day 1 will follow in the same manner as the calculation outlined above for the primary efficacy variable.

- 1b: *Change from baseline in FEV_1 $AUC_{0\text{-}4h}$ normalized by time at Day 1 and Day 14*

The baseline value is the average of the T-45 and T-15 min pre-dose FEV_1 measurements on Day 1. The change from baseline in FEV_1 $AUC_{0\text{-}4h}$ normalized by time at Day 1 and Day 14 will be calculated using the following equation:

$$\left\{\sum_{\mathbf{i}}[(\mathbf{t_i}-\mathbf{t_{i-1}})(\mathbf{FEV1_i}+\mathbf{FEV1_{i-1}})/\mathbf{2}]\right\}/\mathbf{time}$$

Where:

for t_0, $FEV1_0$ is the pre-dose average of T -45' and T -15' before the time of study drug administration at Day 14 or Day 1.

t_0 is the actual time of the administration of the first morning dose of study drug,

for i = 15 min, 30 min, 45 min, 1h, 2h, 3h and 4h, $FEV1_i$ is the actual FEV1 value at each time point and t_i is the actual time of sample i.

time is the actual elapsed time from t_0 until *t4*.

For the calculation, all valid measurements are taken and, in addition, the following imputation rules apply:

- If one of the spirometry 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 (corresponding to time 0 for the calculation of AUC). If no measurement is available, then the pre-dose value will be considered as missing.
- If the pre-dose value is not available, the entire curve will be considered as missing
- The linear trapezoidal rule will allow $AUC_{0\text{-}4h}$ to be calculated if a single, isolated missing value (not pre-dose or last value) exists. This is akin to replacing the missing value by linear interpolation using the adjacent values
- If the value at 4h post-dose is missing, it will be replaced by the value at 3h.
- If two or more consecutive post-dose time points until 4h have a missing observation, the entire FEV_1 $AUC_{0\text{-}4h}$ for that day will be missing.
- If in three or more post-dose time points until 4h have missing values, the FEV_1 $AUC_{0\text{-}4h}$ for that day will be missing.
- In case of missing actual time, the theoretical or planned time is used.

- 1c: *Change from baseline in FEV_1 $peak_{0\text{-}4h}$ at Day 1 and Day 14*

FEV_1 $peak_{0\text{-}4h}$ at Day 1 and Day 14 will be calculated using the following formula:

Maximum value of all FEV_1 values at the time points 15 min, 30 min, 45 min, 1h, 2h, 3h, and 4h of the respective day. In case of less than three missing values among post-dose spirometry measurements at 45min, 1h, 2h, 3h, 4h, the peak value will be calculated as the maximum of the available post-dose values over the time interval considered (4h). In case of three or more missing values, the peak value will be considered as missing.

- 1d: *Change from baseline in pre-dose morning FEV_1 (average of pre-dose FEV_1 measurements) at Day 14.*

If one of the spirometry 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. The baseline value is the average of the T-45 and T-15 min pre-dose FEV_1 measurements on Day 1.

- 2a: *Change from baseline in FVC $AUC_{0\text{-}12h}$ normalized by time at Day 1 and Day 14*

FVC is a continuous variable derived from spirometry data ([redacted]). The baseline value is the average of the pre-dose FVC measurements on Day 1. FVC $AUC_{0\text{-}12h}$ will be calculated on Day 1 and Day 14. The calculation of the FVC $AUC_{0\text{-}12h}$ will follow in the same manner as the calculation outlined above for the primary efficacy variable.

- 2b: *Change from baseline in FVC $AUC_{0\text{-}4h}$ normalized by time at Day 1 and Day 14*

FVC $AUC_{0\text{-}4h}$ will be calculated on Day 1 and Day 14. The baseline value is the average of the pre-dose FVC measurements on Day 1. The calculation of the FVC $AUC_{0\text{-}4h}$ will follow in the same manner as the calculation outlined above for FEV_1 $AUC_{0\text{-}4h}$.

- 2c: *Change from baseline FVC $peak_{0\text{-}4h}$ at Day 1 and Day 14.*

FVC $peak_{0\text{-}4h}$ at Day 1 and Day 14 will be calculated using the following rule:

(Maximum value of all FVC values at the time points 15 min, 30 min, 45 min, 1h, 2h, 3h, and 4h of the respective day).
If 3 or more missing values are reported among the post-dose spirometry measurements at 45 min, 1h, 2h, 3h, 4h, the FVC $peak_{0\text{-}4h}$ for that day will be missing.

- *2d: Change from baseline in pre-dose morning FVC (average of pre-dose FVC measurements) at Day 14.*

The baseline value is the average of the pre-dose FVC measurements on Day 1. If one of the spirometry 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.

- 3: *Time to onset of action (change from baseline in post-dose $FEV_1 \geq 12\%$ and $\geq 200mL$) at Day 1*

In case of at least one post-dose timepoint with change from baseline in $FEV_1 \geq 12\%$ and $\geq 200mL$, then Time to onset of action will be equal to the first post-dose timepoint with change from baseline in $FEV_1 \geq 12\%$ and $\geq 200mL$ in the time interval considered (12 h). Time to onset of action will be calculated as the difference in minutes from the actual spirometry time and the time of the start of dosing. *In case of no time-point with change from baseline in FEV_1 $\geq 12\%$ and $\geq 200mL$, and less than four missing values among post-dose spirometry measurements at 15 min, 30 min, 45 min, 1h, 2h, 3h and 4h, then Time to onset of action will*

be equal to the last available post-dose time-point with non-missing data and the subject will be considered as censored in the analysis. In case of four or more missing values among post-dose spirometry measurements at 15 min, 30 min, 45 min, 1h, 2h, 3h and 4h the subject will be excluded from the analysis of time to onset of action.

7.2.12 Safety Variables

There are 7 sets of safety variables identified in the protocol. A description of each variable, and the timing of the recording of the information is presented below.

- 1: Treatment Emergent Adverse Events (TEAEs)

Three categories of AEs will be presented: Pre-Treatment, Treatment Emergent, and Post-Study. An AE will be classified as:

- Pre-treatment AE: if AE starts after signing the informed consent and before the first randomized study medication intake (AE onset date < date of first randomized study medication intake at the study-level).
- Treatment emergent AEs (TEAEs): all adverse events starting on or after the first study drug intake, up to study completion/discontinuation. TEAEs are defined as AEs with date of first randomized study drug intake at the study-level ≤ AE onset date ≤ date of study completion/discontinuation.
- Post-study AE: if AE starts after the date of completion/discontinuation (AE onset date > date of completion/discontinuation).

TEAEs will be assigned to the last randomized study drug received before the start of the TEAE. Therefore AEs started during the Washout Period will be assigned to the treatment received in the previous Period and AEs started during the Follow-up Period (i.e. from the day after Visit 9 until the date of completion/discontinuation) will be assigned to the treatment received in Treatment Period 4. AEs occurring during the Washout and the Follow-up Periods will be flagged in the listings.

Additional variables to define an adverse event include the following:

- Serious AE (SAE) is defined as any AE that has the question “Is the AE serious?” marked as “Yes” on the eCRF.
- ADR is defined as any AE that has the question “Is the AE Related to Study Drug?” marked as “Yes” on the eCRF.
- Serious ADR is defined as any ADR that are also SAE
- *Severe AE*, defined as any AE that has intensity marked as “Severe” on the eCRF.
- *AE leading to study drug discontinuation*, defined as a TEAE where the action taken on the eCRF is marked as “Drug withdrawn”.
- *AE leading to death*, defined as a TEAE where the outcome is marked as “Fatal” on the eCRF.
- *Relative day of AE onset*, defined as the AE onset date – Date of first study drug intake (of the associated treatment) + 1 if the AE onset date is greater or equal to date of first

study drug intake. For pre-treatment AEs, the relative day is defined as the AE onset date – Date of first study drug intake (study-level). Relative day will not be calculated in case of partial/missing date of AE onset. The relative day of TEAEs is calculated considering the date of first study medication intake in the period associated with the start date of the TEAE.

- *Duration of AE*, defined as the AE end date – AE onset date + 1 when the AE is resolved. If the AE is not resolved, the duration is defined as study completion/discontinuation date – AE onset date + 1. AE duration will not be calculated in the case of a partial/missing date of AE onset.

In case of missing or incomplete AE date 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 date. The AE will be allocated to the first category allowed by the available data, according to the following order:

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

- 2: Vital signs (systolic and diastolic blood pressure)

Blood pressure measurements are continuous variables and recorded in mmHg.

Baseline of Vital signs, as defined in section 7.2.3, will be considered the pre-dose measurement on Day 1 of each Treatment Period. Change from pre-dose on Day 14 will also be evaluated.

- 3: *12-lead ECG parameters (HR, QTcF, QRS, PR)*

12-lead ECG parameters are continuous variables. Heart rate (HR) is recorded in bpm; PR interval, QRS interval and QTcF interval are recorded in msec.
QTc value will be calculated using the Fridericia formula (Fridericia-corrected QTc=$\frac{QT}{\sqrt[3]{RR}}$).
ECG parameters are provided by centralized ECG service provider, in eCRF only data, time and Investigator's Interpretation is collected.

The changes from baseline will be based on the pre-dose assessment on Day 1 of each Treatment Period. Change for pre-dose on Day 14 will also be evaluated.

- 4: *HR AUC_{0-4h} normalized by time.*

HR AUC_{0-4h} will be calculated at Day 1 and Day 14. The calculation of the *HR AUC_{0-4h}* will follow in the same manner as the calculation outlined above for the secondary efficacy variable 1b.

HR AUC_{0-4h} will be calculated only if HR data are recorded on each time-point (pre-dose, and

30 minutes, 1h, 4h post-dose).

- 5: *HR peak$_{0-4h}$*

HR peak$_{0-4h}$ will be calculated on Day 1 and Day 14. *HR peak$_{0-4h}$* will be calculated using the following formula: maximum value of all *HR* values at the time points 30 min, 1h, and 4h of the respective day.

HR peak$_{0-4h}$ will be calculated only if HR data are recorded on each post-dose time-point (30 minutes, 1h, 4h post-dose).

- 6: *Serum potassium and blood glucose*

From Visit 2 to Visit 9, blood samples of about 2.5 mL will be collected for measuring serum Potassium and glucose pre-dose and at 1.5, 3, 5, 7 and 11h post-dose (total blood volume = 15 mL/Visit). The Baseline value is pre-dose measurement on Day 1 of each Treatment Period. Change for pre-dose on Day 14 will also be evaluated.

- *7: Hematology, Chemistry, and Pregnancy Tests*

Blood samples of about 12mL will be collected for hematology and serum chemistry at Screening, Visit 9 and Early Termination in the morning. Data from hematology, chemistry, and Pregnancy Tests will only be listed.

The following evaluations will be performed using a central laboratory:

- *Hematology test: red blood cells count (RBC), white blood cells count (WBC) and differential, total hemoglobin (Hb), hematocrit (Hct), platelets count (PLT).*
- *Serum chemistry test: blood urea nitrogen (BUN), cholesterol, triglycerides, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Gamma-glutamyl transferase (γ-GT), total bilirubin, alkaline phosphatases, albumin, total proteins, and electrolytes (sodium, potassium, calcium, and chloride).*
- *Serum pregnancy test (serum β-hCG) in women of child-bearing potential;* results will be presented as positive or negative.

A urine pregnancy test using a commercial urine hCG pregnancy test strip will be conducted at each visit from V1-V8. Urine β-hCG from these visits will be presented as positive or negative.

Complete Blood Count (abbreviation followed by the full name and units)

HCT:	Hematocrit (L/L)
HGB:	Hemoglobin (g/L)
PLATE:	Platelets (10^9/L)
RBC:	Erythrocytes (10^12/L)
WBC:	Leucocytes (10^9/L)

Differential (abbreviation followed by the full name and units)
BASO: Basophil (10^9/L) and (%)
EOSIN: Eosinophil (10^9/L) and (%)
LYMPH: Lymphocyte (10^9/L) and (%)
MONO: Monocyte (10^9/L) and (%)
NEUT: Neutrophil (10^9/L) and (%)

Blood Chemistry (abbreviation followed by the full name and units)
ALB: Albumin (g/L)
ALKPH: Alkaline Phosphatase (U/L)
ALT: ALT (U/L)
AST: AST (U/L)
BUN: Blood Urea Nitrogen (mmol/L)
BILDIR: Direct Bilirubin (µmol/L)
CA: Calcium (mmol/L)
CHOL: Cholesterol (mmol/L)
CL: Chloride (mmol/L)
CREAT: Creatinine (µmol/L)
GGT: Gamma-GT (U/L)
GLUC: Fasting Serum Glucose (mmol/L)
K: Potassium (mmol/L)
NA: Sodium (mmol/L)
PROT: Total Protein (g/L)
TRIG: Triglycerides (mmol/L)
URATE: Urate (µmol/L)

Results from the central laboratory will include the out of range flag based on the lower and upper limits of normal range. Categories will be

- Low CS
- Low NCS
- Normal
- High NCS
- High CS, and
- Missing.

8 Analysis Methods

8.1 General Methods

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, with p-values for the primary efficacy analysis adjusted for multiplicity as described in Section 8.2.1.5.

General rules to be used for reporting the number of decimal places for derived variables in the listings (in the analyses rounding will not be performed):

- Age at First Asthma Diagnosis (years), BMI, treatment exposure (days): whole numbers;
- Time to discontinuation (weeks), duration of smoking (years), Time since First Asthma Diagnosis (years), compliance, 1 decimal place;
- 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: 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 probabilities).
- hazard ratio and its confidence limits, and its confidence limits: 2 decimal places;
- P-values: 3 decimal places; if the p-value is less than 0.001, it will be presented as <0.001.

In general, additional to the analysis model results presented in TLFs, the full SAS output generated for all the analyses will be presented to the sponsor as a standalone report. SAS output results will be generated only after DB lock.

8.1.1 Rules for Patients Receiving the Same Treatment in Two Periods

For **continuous variables** presented in tables for which both periods are considered for patients receiving the same treatment more than once, summary statistics will include the number of non-missing observations on the patient level ("n"), the number of non-missing observations on the treatment period level ("n periods"), mean, standard deviation, 95% (or otherwise) confidence interval of the mean (only in the efficacy and safety analyses, unless otherwise specified), minimum, median and maximum. The number of treatment periods considered ("n periods") will not be presented in the summary tables on baseline characteristics.
For patients receiving the same treatment in 2 periods, each subject will contribute once to the summary statistics. Since 2 data points will be available, but the subject should only contribute once, the 2 available data points will be averaged for these subjects prior to calculation of the summary statistics for all subjects.

Example:
Parameter: Change from Baseline (CFB) in FEV_1 AUC_{0-12} at Day 14
Patient 123 receives Treatment A in Period 1 and receives Treatment A again in Period 2. The values of CFB in FEV_1 AUC_{0-12} at Day 14 are: Period 1: 100mL, Period 2: 110mL.
For summary statistics of CFB FEV_1 AUC_{0-12} at Day 14 for Treatment A, Patient 123 will contribute one value to the summary statistics of CFB in

FEV_1 AUC_{0-12} at Day 14. The value will be the average of the values from Period 1 and Period 2, which is 105mL.

For **qualitative variables**, the number (n) and percentage (%) of subjects with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Unless otherwise specified, the denominator for each percentage will be the number of non-missing observations within the analysis set and treatment group. For tables in which both periods are considered for patients receiving the same treatment more than once the following percentages will be compute:

- For disposition, protocol deviations, maintained, concomitant medications, and exposure/compliance, the percentages will be based on the number of treatment periods and a footnote will be added to indicate this.
- For safety variables, the percentages will be based on the number of patients in each treatment arm and a footnote will be added to specify this.

For categorical analyses of QTcF, patients receiving a treatment twice will contribute only once to the summary statistics, using the highest QTcF value.
Listings including sequence will present the sequence of treatment allocated by the randomization system. A single listing will also be presented including the sequences based on the original Randomization and Decode Lists (described in Section 10.1, below).

8.1.2 Rules for Handling Missing Data

No adjustment for missing data is carried out. The specific methods to deal with missing data, in particular with partial or missing dates (e.g., of medication use), missing spirometry data and missing questionnaire data, are laid out in detail in the description of the variable derivation in the subsections under Section 7.2.

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

8.2 Specific Methods for Efficacy Analyses

Analyses Based on Mixed Models

Primary efficacy endpoint

Patients receiving the same treatment in more than one period will be included in the primary efficacy model including all available data.

Example: Parameter: Change from Baseline (CFB) in FEV1 AUC0-12 at Day 14 Patient 123 receives Treatment A in Period 1 and receives Treatment A again in Period 2.

For primary analysis of CFB FEV1 AUC0-12 at Day 14 for Treatment A, Patient 123 will contribute two values to the response variable CFB in FEV1 AUC0-12 at Day 14 (one value from Period 1 and another value from Period 2).

● Model for Analysis

Change from baseline in FEV1 $AUC_{0\text{-}12h}$ normalized by time at Day 14 will be analyzed using an Analysis of Covariance (ANCOVA) model including treatment, period and subject as fixed effects and baseline as a covariate.

```
proc mixed data = <xxx>;
 class subject treatment period;
 model <response> = subject  treatment  period fev1base;
 lsmeans treatment / cl ;
 lsmestimate treatment 'Treatment A vs Placebo: Day 14' 1 0 0 0 -1 0,
                       'Treatment B vs Placebo: Day 14' 0 1 0 0 -1 0,
                       'Treatment C vs Placebo: Day 14' 0 0 1 0 -1 0,
                       'Treatment D vs Placebo: Day 14' 0 0 0 1 -1 0
                       / cl adjust=simulate(seed=12311980 acc=0.0001);
 lsmestimate     treatment 'Trt B vs Trt A: Day 14' -1 1 0 0 0 0 / cl;
 lsmestimate     treatment 'Trt C vs Trt A: Day 14' -1 0 1 0 0 0/ cl;
 lsmestimate     treatment 'Trt D vs Trt A: Day 14' -1 0 0 1 0 0/ cl;
 lsmestimate     treatment 'Trt C vs Trt B: Day 14'   0 -1 1 0 0 0 / cl;
 lsmestimate     treatment  'Trt D vs Trt B: Day 14' 0 -1 0 1 0 0/cl;
 lsmestimate     treatment 'Trt D vs Trt C: Day 14' 0 0 -1 1 0 0/cl;
 lsmestimate     treatment 'Trt F vs Placebo: Day 14' 0 0 0 0 -1 1/cl;
run;
```

where:

- *Subject* is the variable identifying subject.
- *treatment* is the randomized treatment variable, codified and sorted as follow:
    1. Treatment A (FF 6 µg/d)
    2. Treatment B (FF 12 µg/d)
    3. Treatment C (FF 24 µg/d)
    4. Treatment D (FF 48 µg/d)
    5. Placebo
    6. Treatment F (PERFOROMIST® 40 µg/d)
- *period* is the period variable (Treatment Period 1, Treatment Period 2, Treatment Period 3, Treatment Period4)
- *fev1base* is the baseline FEV_1 result

The adjusted means in each treatment group, the adjusted mean difference between treatments, their 95% Confidence Intervals (CIs) and their p-values at Day 14 will be estimated by the model. In addition, the p-values for each of the factors in the model will be provided.

The CIs and the p-values of the comparisons between each dose of CHF 1531pMDI and placebo will be adjusted for multiplicity. The adjustment will be based on the parametric simulation

method by Edwards and Berry (adjust=simulate in the MODEL statement). The random number seed will be set equal to 12311980, and 0.0001 will be used for the target accuracy radius gamma (i.e. ACC=0.0001). At each dose level, the superiority of CHF 1531 pMDI will be demonstrated by a **statistically significant** difference (adjusted p-value < 0.05) favoring CHF 1531 pMDI.

The adjusted mean pairwise differences between treatments A, B, C, and D and their 95% Confidence Intervals (CIs) will be estimated by the model, comparing each dose with a lower dose and treatment F versus placebo. The CIs and the p-values of the comparisons between each pairwise comparisons at Day 14 will not be adjusted for multiplicity.

Sensitivity Analyses for the primary efficacy variable

Additional sensitivity analyses will be performed on the primary efficacy endpoint only.

Sensitivity Analysis 1: Incorporating Only the First Instance of Each Treatment

Patients receiving the same treatment in more than one period will be included in the primary efficacy model including only data from the first instance of each treatment.

Example: Parameter: Change from Baseline (CFB) in FEV1 AUC0-12 at Day 14 Patient 123 receives Treatment A in Period 1 and receives Treatment A again in Period 2. For Sensitivity Analysis 1 of CFB FEV_1 AUC_{0-12} at Day 14 for Treatment A, Patient 123 will contribute one value to the response variable CFB in FEV_1 AUC_{0-12} at Day 14. The value will be the result from Period 1. The result obtained for Patient 123 during Period 2 will be ignored (considered as missing) for this sensitivity analysis.

Sensitivity Analysis 2: Incorporating Only Treatment Periods for Which Treatment was Assigned After the IRT System Update

Following the IRT system update on [redacted], the treatment allocation was changed for all patients. Of note, the majority of treatment assignments occurred after the update to the randomization system on [redacted]. The file used after [redacted] would have provided an appropriate randomization had it been applied consistently across all patients. With this in mind, the following sensitivity analysis is planned.

The primary analysis will be repeated, incorporating only treatment periods for which treatment was allocated on or after [redacted]. Treatment periods for which treatment was allocated prior to [redacted] will be excluded from the analysis. Of note, the system update occurred at [redacted] in the US Eastern time zone. No allocation was performed on [redacted] prior to the update. Therefore, allocations occurring on [redacted] all occurred after the update.

Example:

Parameter: Change from Baseline (CFB) in FEV1 AUC0-12 at Day 14

Patient 123 receives Treatment A in Period 1 and receives Treatment A again in Period 2. The treatment allocation for period 1 occurred prior to [redacted] The treatment allocation for Period 2 occurred after

For Sensitivity Analysis 2 of CFB FEV1 AUC0-12 at Day 14 for Treatment A, Patient 123 will contribute one values to the response variable CFB in FEV1 AUC0-12 at Day 14. The value will be the result from Period 2. The result obtained for Patient 123 during Period 1 will be ignored (considered as missing) for this sensitivity analysis.

Sensitivity Analysis 3: Incorporating Subject as a Random Effect

The primary analysis will be repeated, incorporating subject as a random effect. As the period-level baseline value is included as a covariate in the model, the approach proposed by Kenward and Roger (Kenward MG, Roger JH. The use of baseline covariates in crossover studies. Biostatistics. 2010 Jan;11(1):1-17) was adopted. This model assumes a joint multivariate normal distribution for Zik = (Xik1, Yik1, Xik2, …, Xikp, Yikp)T, where Xikp and Yikp denote the baseline measurement and the response, respectively, from the kth subject in sequence i in period p. The covariance matrix of Zik is given by:

$V(\mathbf{Z}_{ik}) = \mathbf{\Sigma_W} \otimes \mathbf{I}_{\boldsymbol{p}} + \mathbf{\Sigma_B} \otimes \mathbf{J}_{\boldsymbol{p}}$.

Ip and Jp denote the p x p identity matrix and matrix of ones, respectively. $\mathbf{\Sigma_W}$ represents the covariance matrix for X and Y within a treatment period and $\mathbf{\Sigma_B}$ the covariance matrix between baseline and response at the subject level. Two unstructured covariance matrices are assumed for $\mathbf{\Sigma_W}$ and $\mathbf{\Sigma_B}$:

$$\mathbf{\Sigma_W} = \begin{pmatrix} \boldsymbol{\sigma_{xx}} & \boldsymbol{\sigma_{xy}} \\ \boldsymbol{\sigma_{xy}} & \boldsymbol{\sigma_{yy}} \end{pmatrix} \quad \text{and} \quad \mathbf{\Sigma_B} = \begin{pmatrix} \boldsymbol{\eta_{xx}} & \boldsymbol{\eta_{xy}} \\ \boldsymbol{\eta_{xy}} & \boldsymbol{\eta_{yy}} \end{pmatrix}.$$

The model includes a fixed period effect with 2p levels, one for each element of Z, and a fixed treatment effect that applies to the Ys only.

The following SAS code will be used for this sensitivity analysis:

```
proc mixed data=<XXX>;
        class subject treatment period type;
        model <response> = period*type treatment*type / ddfm=kr;
        random type / subject=subject type=un;
        repeated type / subject=subject*period type=un;
        lsmestimate treatment*type 'Chg from baseline: Treatment A'   -1 1 0 0 0 0 0,
                                   'Chg from baseline: Treatment B'   -1 0 1 0 0 0 0,
                                   'Chg from baseline: Treatment C'   -1 0 0 1 0 0 0,
                                   'Chg from baseline: Treatment D'   -1 0 0 0 1 0 0,
                                   'Chg from baseline: Placebo' -1 0 0 0 0 1 0,
                                   'Chg from baseline: Treatment F'   -1 0 0 0 0 0 1 / cl;
        lsmestimate treatment*type          'Treatment A vs Placebo' 0 1 0 0 0 -1 0,
                                            'Treatment B vs Placebo' 0 0 1 0 0 -1 0,
```

```
                                        'Treatment C vs Placebo' 0 0 0 1 0 -1 0,
                                        'Treatment D vs Placebo' 0 0 0 0 1 -1 0
                                / cl adjust=simulate(seed=12311980 acc=0.0001);
        lsmestimate     treatment*type 'Trt B vs Trt A: Day 14'    0 -1 1 0 0 0 0/cl;
        lsmestimate     treatment*type 'Trt C vs Trt A: Day 14'    0 -1 0 1 0 0 0/cl;
        lsmestimate     treatment*type 'Trt D vs Trt A: Day 14'    0 -1 0 0 1 0 0/cl;
        lsmestimate     treatment*type 'Trt C vs Trt B: Day 14'    0 0 -1 1 0 0 0/cl;
        lsmestimate     treatment*type 'Trt D vs Trt B: Day 14'    0 0 -1 0 1 0 0/cl;
        lsmestimate     treatment*type 'Trt D vs Trt C: Day 14'    0 0 0 -1 1 0 0/cl;
        lsmestimate     treatment*type 'Treatment F vs Placebo'    0 0 0 0 0 -1 1/cl;
run;
```

where:

- *subject* is the variable identifying subject
- *treatment* is the variable identifying the baseline measurement and the randomized treatment, codified and sorted as follow:
    - 0: baseline FEV_1 measurement (irrespective of the treatment assigned in the period)
    - 1: Treatment A (FF 6 µg/d)
    - 2: Treatment B (FF 12 µg/d)
    - 3: Treatment C (FF 24 µg/d)
    - 4: Treatment D (FF 48 µg/d)
    - 5: Placebo
    - 6: Treatment F (PERFOROMIST® 40 µg/d)
- *period* is the period variable (Treatment Period 1, Treatment Period 2, Treatment Period 3, Treatment Period 4)
- *type* is a variable identifying the baseline measurement and the response, codified as follow:
    - 0: baseline FEV_1 measurement
    - 1: response (FEV_1 AUC_{0-12} at Day 14).

For each treatment period, the input data set for the MIXED procedure will include two records, as in the example below. The first record will include the baseline FEV_1 measurement in the period, with treatment = 0 and type = 0. The second record will include the response (FEV_1 AUC_{0-12} at Day 14) in the period, with treatment = treatment assigned in the period and type = 1.

Subject	Period	Treatment	Type	Value
001	2	0	0	xx.x

001	2	5	1	yy.y

Secondary efficacy endpoints

For secondary efficacy analyses the comparisons between treatments will be performed with no multiplicity adjustment. All the secondary efficacy variables except for Time to onset of action (i.e., change from baseline in post-dose $FEV_1 \geq 12\%$ and ≥ 200 mL) at Day 1 will be analyzed using the same model as the one used for the primary efficacy analysis.

In case of patients receiving the same treatment in more than one period, the same approach will be used as for the primary efficacy analysis (including all available data).

The SAS code for the secondary efficacy endpoints will be:

```
proc mixed data = <xxx>;
  class subject treatment period;
  model <response> = subject  treatment  period fev1base ;
  lsmeans treatment / cl;
  lsmestimate 'Trt A vs Placebo: day 1' treatment 1 0 0 0 -1 0;
  lsmestimate 'Trt B vs Placebo: day 1' treatment 0 1 0 0 -1 0;
  lsmestimate 'Trt C vs Placebo: day 1' treatment 0 0 1 0 -1 0;
  lsmestimate 'Trt D vs Placebo: day 1' treatment 0 0 0 1 -1 0;
  lsmestimate treatment 'Trt B vs Trt A: day 1' -1 1 0 0 0 0;
  lsmestimate treatment 'Trt C vs Trt A: day 1'     -1 0 1 0 0 0;
  lsmestimate treatment 'Trt D vs Trt A: day 1'     -1 0 0 1 0 0;
  lsmestimate treatment 'Trt C vs Trt B: day 1'    0 -1 1 0 0 0;
  lsmestimate treatment 'Trt D vs Trt B: day 1'    0 -1 0 1 0 0;
  lsmestimate treatment 'Trt D vs Trt C: day 1'    0 0 -1 1 0 0;
  lsmestimate treatment 'Trt F vs Placebo: day 1' 0 0 0 0 -1 1;
run;
```

- *Subject* is the variable identifying subjects.
- *treatment* is the randomized treatment variable, codified and sorted as follow:
    1. Treatment A (FF 6 µg/d)
    2. Treatment B (FF 12 µg/d)
    3. Treatment C (FF 24 µg/d)
    4. Treatment D (FF 48 µg/d)
    5. Placebo
    6. Treatment F (PERFOROMIST® 40 µg/d)
- *period* is the period variable (Treatment Period 1, Treatment Period 2, Treatment Period 3, Treatment Period 4).
- *fev1base* is the baseline FEV_1 result

The adjusted means in each treatment group, the adjusted mean difference between treatments, their 95% Confidence Intervals (CIs) and their p-values will be estimated by the model. In addition, the p-values for each of the factors in the model will be provided.The CIs and the p-values of the comparisons between treatments at Day 1 or Day 14, depending on with secondary variables we are analyzing, will not be adjusted for multiplicity.

Analyses Based on the Time to Onset

Analyses based on time to onset will include only data from the first instance of each treatment for patients receiving the same treatment twice.

Example:

Parameter: Time to Onset of Action (Change from Baseline in Post-dose FEV1 ≥ 12% and ≥ 200 ml) on Day 1

Patient 123 receives Treatment A in Period 1 and receives Treatment A again in Period 2.

For analysis of Time to Onset of Action (Change from Baseline in Post-dose FEV1 ≥ 12% and ≥ 200 ml) on Day 1 for Treatment A, Patient 123 will contribute one values to the response variable. The value will be the result from Period 1. The result obtained for Patient 123 during Period 2 will be ignored (considered as missing) for this analysis.

A Cox proportional hazards model will be utilized to analyze the time to onset of action in FEV_1 (i.e., change from baseline in post-dose FEV_1 ≥ 12% and ≥ 200 mL). The Cox proportional hazards model will be stratified by subject and will include treatment and period as a factor, and baseline FEV_1 as covariate. The generic code for the Cox model is:

```
proc phreg data=<xxx>;
  class  treatment  period subject ;
  model time*censor(0) = treatment period fev1base / risklimits ties=exact;
 strata subject;  contrast treatment “Treatment A vs. Placebo"        1 0 0 0 -1 /estimate=exp;
 contrast treatment “Treatment B vs. Placebo"        0 1 0 0 -1 /estimate=exp;
 contrast treatment “Treatment C vs. Placebo"        0 0 1 0 -1 /estimate=exp;;
 contrast treatment “Treatment D vs. Placebo"        0 0 0 1 -1 /estimate=exp;
 contrast treatment “Treatment B vs. Treatment A" -1 1 0 0 0 /estimate=exp;
 contrast treatment “Treatment C vs. Treatment A" -1 0 1 0 0 /estimate=exp;
 contrast treatment “Treatment D vs. Treatment A" -1 0 0 1 0 /estimate=exp;
 contrast treatment “Treatment C vs. Treatment B" 0 -1 1 0 0 /estimate=exp;
 contrast treatment “Treatment D vs. Treatment B" 0 -1 0 1 0 /estimate=exp;
 contrast treatment “Treatment D vs. Treatment C" 0 0 -1 -1 0/estimate=exp;
 contrast treatment “Treatment F vs. Placebo"        0 0 0 0 -1 /estimate=exp;
run;
```

The generic code for the Kaplan-Meier plot is:

```
proc lifetest data=<xxx>;
    time time*censor(0);
    strata treatment;
run;
```

where:

- *Subject* is the subject variable.

- *treatment* is the randomized treatment variable, codified and sorted as follow:
    1. Treatment A (FF 6 µg/d)
    2. Treatment B (FF 12 µg/d)
    3. Treatment C (FF 24 µg/d)
    4. Treatment D (FF 48 µg/d)
    5. Placebo
    6. Treatment F (PERFOROMIST® 40 µg/d)
- *fev1base* is the baseline FEV_1 result
- *period* is the visit period variable (Treatment Period 1, Treatment Period 2, Treatment Period 3, Treatment Period4).

A censor variable value of 0 will be used for subjects who do not experience the onset of action in FEV_1. If the option ties=exact requires a considerable amount of computer resources, the Efron approximation will be used (ties=efron).

The 1st quartile, median, and 3rd quartile for the time to onset of action in FEV_1 (i.e., change from baseline in post-dose $FEV_1 \geq 12\%$ and ≥ 200 mL) will be provided along with the number and percentage of subjects who were censored. The hazard ratios, 95% confidence intervals for the hazard-ratios, and p-values comparing each pair of treatments will be provided. P-values will not be adjusted for multiplicity. In addition, the p-values for each of the factors in the model will be provided.

8.2.1 Statistical/Analytical Issues

8.2.1.1 Adjustments for Covariates

All linear models and time to event models will be adjusted for subject (used as a stratum in the Cox proportional hazards model), period and baseline value as covariate.

8.2.1.2 Handling of Dropouts or Missing Data

The rules to address missing data rules for specific variables are described in Section 7.2 and 8.1.2.

8.2.1.3 Blind Review

A Blind Data Review Meeting is organized just before data base lock to finalize the list of protocol deviations which will exclude subjects from the Per Protocol analysis and also to address handling of any outstanding data issues. The Data Review Report will describe all agreed handling and will be finalized prior to data base lock and unblinding. The Data Review Plan will describe the tables, listings and figures used during this meeting, and falls outside the scope of the SAP.

8.2.1.4 Multi-center Studies

As all the analyses will be based on within-subject comparisons, no adjustment is done for the multiple centers, and no analysis per center is carried out.

8.2.1.5 Multiple Comparisons/Multiplicity

Adjustment for multiplicity is applied only to the primary efficacy analysis. The CIs and the p-values of the comparisons between each dose of CHF 1531pMDI and placebo for the primary efficacy endpoint at Day 14 will be adjusted for multiplicity. The adjustment will be based on the parametric simulation method by Edwards and Berry. At each dose level, the superiority of CHF 1531 pMDI will be demonstrated by a **statistically significant** difference (adjusted p-value < 0.05) favoring CHF 1531 pMDI.

8.3 Specific Methods for Safety Analyses

Analyses Based on ANCOVA

The change from baseline (pre-dose measurement on Day 1 of each treatment period) and the change from pre-dose on Day 14 (only for Day 14 post-dose time points) in post-dose 12-lead ECG parameters (HR, QTcF, QRS and PR) will be analyzed using an ANCOVA model for each time point including treatment, period and subject as fixed effects and baseline (pre-dose measurement on Day 1 of each treatment period/ change from pre-dose on Day 14) as a covariate. The SAS code will be:
In case of patients receiving the same treatment in more than one period the same approach will be used as for the primary efficacy analysis (including all available data).

```
proc mixed data = <xxx>;
  class subject treatment period
  model <response> = subject  treatment  period base  /
  lsmeans treatment / cl alpha=0.10;
  lsmestimate 'Trt A vs Placebo: day 1' treatment 1 0 0 0 -1 0/ cl alpha=0.10,
  lsmestimate 'Trt B vs Placebo: day 1' treatment 0 1 0 0 -1 0/ cl alpha=0.10,
  lsmestimate 'Trt C vs Placebo: day 1' treatment 0 0 1 0 -1 0/ cl alpha=0.10,
  lsmestimate 'Trt D vs Placebo: day 1' treatment 0 0 0 1 -1 0/ cl alpha=0.10,
  lsmestimate 'Trt B vs Trt A: day 1' treatment    -1 1 0 0 0 0/ cl alpha=0.10,
  lsmestimate 'Trt C vs Trt A: day 1' treatment    -1 0 1 0 0 0/ cl alpha=0.10,
  lsmestimate 'Trt D vs Trt A: day 1' treatment    -1 0 0 1 0 0/ cl alpha=0.10,
  lsmestimate 'Trt C vs Trt B: day 1' treatment    0 -1 1 0 0 0/ cl alpha=0.10,
  lsmestimate 'Trt D vs Trt B: day 1' treatment    0 -1 0 1 0 0/ cl alpha=0.10,
  lsmestimate 'Trt D vs Trt C: day 1' treatment    0 0 -1 1 0 0/ cl alpha=0.10,
  lsmestimate 'Trt F vs Placebo: day 1' treatment 0 0 0 0 -1 1/ cl alpha=0.10,
run;
```

where:

- *Subject* is the variable identifying subject .
- *treatment* is the randomized treatment variable, codified and sorted as follow:
    1. Treatment A (FF 6 µg/d)
    2. Treatment B (FF 12 µg/d)
    3. Treatment C (FF 24 µg/d)
    4. Treatment D (FF 48 µg/d)

5. Placebo
6. Treatment F (PERFOROMIST® 40 µg/d)

- *period* is the period variable (Period 1, Period 2, Period 3, Period4).)
- *base* is the baseline value (pre-dose measurement on Day 1 of each Treatment Period).

The adjusted means in each treatment and the adjusted mean differences between treatments will be estimated by the model with 90% CIs and their p-values. In addition, the p-values for each of the factors in the model will be provided. The CIs and the p-values of the comparisons between treatments at Day 1 or Day 14, depending on with secondary variables we are analyzing, will not be adjusted for multiplicity.

9 Interim analyses

Not applicable.

10 Overview of Tables, Listings and Figures

Demographics, Asthma history, Pre-Study Smoking Habits, spirometry and reversibility will be presented using all three populations (ITT, Safety, PP). Medical history/concomitant diseases and compliance with study treatment will be presented using the ITT and Safety populations. Medications, ACQ score, compliance use of diary, and protocol deviations will be presented using the ITT population. Vital signs, 12 lead ECG, AEs and laboratory data will be presented using the Safety population.

Since 32 treatment sequences were used in the randomization, no table will be presented by treatment sequence.
Listings including sequence will present the sequence of treatment allocated by the randomization system. All listings will be sorted by patient ID, rather than sequence.

10.1 Disposition of Subjects

A summary of the number of screened subjects, the number of screening failures and reasons for screening failure will be produced for all enrolled subjects.

A disposition summary of subjects will include the number (N) of subjects randomized with the number (n) and percentage (%) of subjects who completed or discontinued the study.

A subject is considered as completed if the Study Termination Form in the eCRF has "Completed" checked for the question "Specify the subject's status". All percentages will be based on the number of subjects randomized.

The reasons for study discontinuation and number of subjects attending each study visit will be summarized overall (including all treatment sequences), using absolute counts and percentages,

based on the number of subjects randomized.
A disposition summary of subjects will also be presented on period-level (counting each treatment period once and including the number of periods as the denominator). It will include both the number of patients ("n") and the number of periods ("n periods") with the percentage (%) of subjects who completed or discontinued the period based on the number of periods. For discontinuations occurring during a wash-out period, treatment assignment will be based on the most-recent treatment received prior to the discontinuation. The reasons for study discontinuation will be also summarized in the same way, using absolute counts and percentages.

The time to discontinuation from study will be summarized overall using descriptive statistics.

A listing will be presented to show the original intended randomization schedule and how it differs from the randomization which was actually implemented by the randomization system and the treatments administered. This listing will include columns for the original intended treatment assignment for each period, the actual treatment assigned by the IRT system for each period, the actual treatment administered/dispensed to the patient, a flag to highlight discrepancies between the intended treatment assignment and the actual treatment assignment, and a flag to highlight discrepancies between the actual treatment assignment and the treatment administered/dispensed to the patient.

10.2 Protocol Deviations

The number of subjects who had at least one Major Protocol Deviation in a treatment period ("Number of Treatment Periods with at Least One Major Deviation") and all Major Protocol Deviations will be summarized by absolute counts (n) and percentages (%) by study treatment for the ITT population. Patients receiving a treatment twice will be considered twice in the corresponding column. Percentages will be based on the number of treatment periods ("n periods") that will also be reported.

When summarized by study treatment, Major Protocol Deviations will be assigned to the last study treatment received prior to the Major Protocol Deviation.

The summary will be repeated for Minor Protocol Deviations.

10.3 Analysis Sets

The number of subjects in each population (each patient counted only once, regardless of the number of periods) will be summarized by absolute counts (n) and percentages (%) for each treatment group across periods and overall. Percentages will be based on the number of treatment periods which were assigned by the randomization system. The number of periods ("n periods") will be also summarized by treatment group by absolute counts ("n periods") for each treatment group.

10.4 Demographic and Other Baseline Characteristics

10.4.1 Demographic Characteristics, Asthma History, and Smoking Habits

Demographic data, Asthma history and smoking habits will be summarized by summary statistics and absolute counts (n) and percentages (%) by treatment sequence and overall for the Safety population, the ITT population and PP population. Tables will be presented overall only

10.4.2 Medical History

Medical and Surgical History and Concomitant Diseases will be summarized on a per-subject basis (i.e. if a subject reported the same event repeatedly the event will be counted only once at the specific level of display). Absolute counts (n) and percentages (%) will be presented for the number of subjects with at least one Medical or Surgical History or Concomitant Disease, and per SOC and per PT within SOC, for the ITT and Safety population. Percentages will be based on the number of subjects in the population. Medical and Surgical History and Concomitant Diseases will be presented overall only.

10.4.3 Baseline Subject Characteristics

Central spirometry and reversibility test data, will be summarized at Visits 1 and 2 with summary statistics and absolute counts (n) for the Safety population, the ITT population and PP population. Central spirometry and reversibility test will be presented overall only.

ECG results at Visit 1 and Vital signs at Visits 1 and 2 will be summarized with summary statistics and absolute counts (n) and percentages (%) for the Safety population. Results will be presented overall only.

ACQ score will be summarized at Visits 1 and 2 with summary statistics and absolute counts (n) using the ITT population. ACQ score will be presented overall only.

Physical examination results will only be listed.

10.4.4 Previous, Maintained and Concomitant Medications

Previous medications will be presented overall, while concomitant medications and maintained medications will be summarized by treatment and overall (for the assignment of medications to a treatment, see section 7.2.6). For concomitant medications and maintained medications, patients receiving the same treatment during two different periods will be considered twice in the corresponding group and the number of periods (“n periods”) will be also reported.

All previous medications will be presented in the tables and the listings.

Post-treatment medications and medications taken only during washout will be only presented in a listing.

Previous, maintained and concomitant medications will be summarized on the ITT population according to Anatomical Main Group (1st level of ATC), Therapeutic Subgroup (2nd level of ATC), Chemical Subgroup (4th level of ATC) and preferred name.

Absolute counts (n) and percentages (%) will be presented for the number of subjects taking at least one medication, and per Anatomical Main Group and per Therapeutic Subgroup within

Anatomical Main Group and per Chemical Subgroup within Therapeutic Subgroup, for the ITT population. The number of subjects ("n") and the number of periods ("n periods") will be presented. Percentages will be calculated based on the number of periods ("n periods") for Concomitant and Maintained medications.

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10.5 Study drug / Investigational Medicinal Product

10.5.1 Background ICS medication

Daily dose of previous ICS treatment for asthma will be summarized by descriptive statistics using absolute counts (n) and percentages (%) of subjects according to the dose category (Low Daily Dosage and Medium Daily Dosage), for the ITT population.

In addition, daily dose of previous ICS treatment for Asthma in term of estimated clinically comparable daily dose of QVAR® and the number of morning and evening puffs that the subject was instructed to take, both for QVAR 40 µg and QVAR 80 µg will be summarized with summary statistics and absolute counts (n) for the ITT population. The table will be presented overall only.

Exposure and compliance will be summarized overall (including all patients together) by summary statistics and absolute counts (n) for the run-in for the ITT population.

During the treatment periods and the Washout period, exposure and compliance will be summarized by summary statistics and absolute counts (n) by treatment for the ITT population. Patients receiving a treatment twice will be considered twice in the corresponding group. The number of patients ("n) and also the number of periods ("n periods") will be reported.

In addition, for all periods, the number and percentage of subjects with satisfactory (65% - 135%) and unsatisfactory (<65%; >135%) levels of compliance to the study drug will be summarized. For treatment periods and Washout Periods, percentages will be based on the number of periods ("n periods") while for run-in period, percentages will be based on the number of subjects in the ITT population. The summary will be repeated by the following compliance categories: ([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%] and > 140%).

10.5.2 Study drug

Treatment exposure and compliance during the Treatment Periods will be summarized by summary statistics and absolute counts (n) by treatment using the ITT population and the Safety population. In addition the number and percentage of subjects with satisfactory (65% - 135%) and unsatisfactory (<65%; >135%) levels of compliance to the study drug will be summarized by treatment using the ITT population and the Safety Population. The summary will be repeated by the following compliance categories ([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%] and > 140%). Patients receiving a treatment twice

will be considered twice in the corresponding group. The number of periods ("n periods") will be also reported. Percentages will be based on the number of periods ("n periods").

10.5.3 Compliance with the use of Diary

Compliance with the use of Diary in Run-in Period will be summarized by summary statistics and absolute counts (n) using the ITT population. In addition the number and percentage of subjects with the following compliance categories ([0%-10%], (10%-20%], (20%-30%], (30%-40%], (40%-50%], (50%-60%], (60%-70%], (70%-80%], (80%-90%], (90%-100%]) will be summarized using the ITT population.

Compliance with the use of Diary in treatment and Washout periods will be summarized by summary statistics and absolute counts (n)by treatment using the ITT population. In addition the number and percentage of subjects with the following compliance categories ([0%-10%], (10%-20%], (20%-30%], (30%-40%], (40%-50%], (50%-60%], (60%-70%], (70%-80%], (80%-90%], (90%-100%]) will be summarized by treatment using the ITT population. Patients receiving a treatment twice will be considered twice in the corresponding group. The number of periods ("n periods") will be also reported. Percentages will be based on the number of periods ("n periods").

10.6 Efficacy Results

10.6.1 Primary efficacy variable

FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 14 and change from baseline in FEV_1 $AUC_{0\text{-}12h}$ will be summarized with summary statistics with the 95% CI of the mean, number of treatment periods considered ("n periods") and number of patients ("n") by treatment for the ITT and the PP population. For patients receiving the same treatment in 2 periods, each subject will contribute once to the summary statistics. Since 2 data points will be available, but the subject should only contribute once, the 2 available data points will be averaged for these subjects prior to calculation of the summary statistics for all subjects.

The primary endpoint is the change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 14.The change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time will be analyzed using an Analysis of Covariance (ANCOVA) as outlined in Section 8.2. The adjusted means in each treatment group and their corresponding 95% confidence intervals (CI), the adjusted mean difference between treatments (active – placebo) and their 95% CIs will be estimated by the model. The CIs and the p-values of the comparisons between each dose of CHF 1531 pMDI and placebo at Day 14 will be adjusted for multiplicity. The adjustment will be based on the parametric simulation method by Edwards and Berry. At each dose level, the superiority of CHF 1531 pMDI versus placebo will be demonstrated by a statistically significant difference (adjusted p-value < 0.05) favoring CHF 1531 pMDI. The adjusted mean pairwise differences between treatments A, B, C, and D and their 95% Confidence Intervals (CIs) will be estimated by the model, comparing each dose with a lower dose and treatment F versus placebo. The CIs and the p-values of the comparisons between each pairwise comparisons at Day 14 will not be

adjusted for multiplicity. In addition, the p-values for each of the factors in the model will be displayed.

The analysis will be performed using the ITT population (primary analysis) and will be repeated using the PP population.

The primary analysis will be repeated for the three sensitivity analysis, as described in section 8.2.

The mean absolute FEV1 and the mean change from baseline at each time pointat Day 1 and Day 14 will be summarized with summary statistics with the 95% CI of the mean and absolute counts (n) and number of treatment periods considered ("n periods") by treatment for the ITT and the PP population. For patients receiving the same treatment in 2 periods, each subject will contribute once for each time point to the summary statistics. Since 2 data points will be available for each time point, but the subject should only contribute once, the 2 available data points will be averaged for these subjects prior to calculation of the summary statistics for all subjects at each time point. The mean absolute FEV_1 and the mean change from baseline at each time point will be plotted for each of the treatment groups at Day 1 and Day 14. These figures will be based on data from subjects in both ITT and PP populations (separate graphs for ITT and PP).

10.6.2 Secondary efficacy variables

The following secondary efficacy endpoints will be summarized using descriptive statistics with the 95% CI of the mean and will be presented by treatment for the ITT population. For patients receiving the same treatment in 2 periods, each subject will contribute once to the summary statistics. Since 2 data points will be available, but the subject should only contribute once, the 2 available data points will be averaged for these subjects prior to calculation of the summary statistics for all subjects. In addition to the summary statistics also the number of treatment periods considered ("n periods") will be reported.
The following analyses will be performed. There will be no adjustment for multiplicity to the CIs or the p-values for any of the secondary efficacy endpoints.

Analysis of Secondary Efficacy Variable 1a: *Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Day 1*

The change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time on Day 1 will be analyzed using an ANCOVA model as outlined in Section 8.2. The adjusted means in each treatment group with their corresponding 95% Cis , and the adjusted mean difference between treatments with their corresponding 95% CIs will be estimated by the model. In addition, the p-values for each of the factors in the model will be displayed.

Analysis of Secondary Efficacy Variable 1b: *Change from baseline in FEV_1 $AUC_{0\text{-}4h}$ normalized by time at Day 1 and Day 14*

The change from baseline in FEV_1 $AUC_{0\text{-}4h}$ normalized by time on Day 1 and Day 14 will be analyzed using an ANCOVA model as outlined in Section 8.2. The adjusted means in each treatment group with their corresponding 95% CIs, and the adjusted mean difference between

treatments with their corresponding 95% CIs will be estimated by the model. In addition, the p-values for each of the factors in the model will be displayed.

Analysis of Secondary Efficacy Variable 1c: *Change from baseline in FEV_1 $peak_{0-4h}$ normalized by time at Day 1 and Day 14.*

The change from baseline in FEV_1 $peak_{0-4h}$ normalized by time on Day 1 and Day 14 will be analyzed using an ANCOVA model as outlined in Section 8.2. The adjusted means in each treatment group with their corresponding 95% CIs, and the adjusted mean difference between treatments with their corresponding 95% CIs will be estimated by the model. In addition, the p-values for each of the factors in the model will be displayed.

Analysis of Secondary Efficacy Variable 1d: *Change from baseline in pre-dose morning FEV_1 (average of pre-dose FEV_1 measurements) Day 14*

The change from baseline in pre-dose morning FEV_1 normalized by time at Day 14 will be analyzed using an ANCOVA model as outlined in Section 8.2. The adjusted means in each treatment group with their corresponding 95% CIs, and the adjusted mean difference between treatments with their corresponding 95% CIs will be estimated by the model. In addition, the p-values for each of the factors in the model will be displayed.

Analysis of Secondary Efficacy Variable 2a: *Change from baseline in FVC AUC_{0-12h} normalized by time at Day 1 and Day 14*

The change from baseline in FVC AUC_{0-12h} normalized by time on Day 1 and Day 14 will be analyzed using an ANCOVA model as outlined in Section 8.2. The adjusted means in each treatment group with their corresponding 95% CIs, and the adjusted mean difference between treatments with their corresponding 95% CIs will be estimated by the model. In addition, the p-values for each of the factors in the model will be displayed.

The mean absolute FVC and the mean change from baseline at each time point at Day 1 and Day 14 will be summarized with summary statistics with the 95% CI of the mean and absolute counts (n) by treatment for the ITT population. . For patients receiving the same treatment in 2 periods, each subject will contribute once for each time point to the summary statistics. Since 2 data points will be available for each time point, but the subject should only contribute once, the 2 available data points will be averaged for these subjects prior to calculation of the summary statistics for all subjects at each time point. The mean absolute FVC and the mean change from baseline at each time point will be plotted for each of the treatment groups at Day 1 and Day 14 for the ITT population.

Analysis of Secondary Efficacy Variable 2b: *Change from baseline in FVC AUC_{0-4h} normalized by time at Day 1 and Day 14*

The change from baseline in FVC AUC_{0-4h} normalized by time on Day 1 and Day 14 will be analyzed using an ANCOVA model as outlined in Section 8.2. The adjusted means in each treatment group with their corresponding 95% CIs, and the adjusted mean difference between

treatments with their corresponding 95% CIs will be estimated by the model. In addition, the p-values for each of the factors in the model will be displayed.

Analysis of Secondary Efficacy Variable 2c: *Change from baseline in FVC peak$_{0\text{-}4h}$ at Day 1 and Day 14*

The change from baseline in FVC peak$_{0\text{-}4h}$ normalized by time on Day 1 and Day 14 will be analyzed using an ANCOVA model as outlined in Section 8.2. The adjusted means in each treatment group with their corresponding 95% CIs, and the adjusted mean difference between treatments with their corresponding 95% CIs will be estimated by the model. In addition, the p-values for each of the factors in the model will be displayed.

Analysis of Secondary Efficacy Variable 2d: • *Change from baseline in pre-dose morning FVC at Day 14.*

The change from baseline in in pre-dose morning FVC at Day 14 will be analyzed using an ANCOVA model as outlined in Section 8.2. The adjusted means in each treatment group with their corresponding 95% CIs, and the adjusted mean difference between treatments with their corresponding 95% CIs will be estimated by the model. In addition, the p-values for each of the factors in the model will be displayed.

Analysis of Secondary Efficacy Variable 3a: *Time to onset of action (change from baseline in post-dose FEV$_1$ ≥ 12% and ≥ 200 ml) at Day 1 (min)*

Time to onset of action (i.e., change from baseline in post-dose $FEV_1 \geq 12\%$ and ≥ 200 ml at Day 1) will be analyzed using a Cox proportional hazard model as outlined in Section 8.2. The 1st quartile, median, and 3rd quartile for the time to onset of action in FEV_1 with their corresponding 95% CIs will be provided along with the number and percentage of subjects who were censored. The hazard ratios, 95% confidence intervals for the hazard-ratios, and p-values comparing treatments will be provided. In addition, the p-values for each of the factors in the model will be provided.

A Kaplan-Meier plot of the survival curves will also be presented.

A summary of the number and percentage of subjects who achieved the threshold at each post-dose time point on Day 1 will be provided.

10.6.3 Other efficacy variables

PEF and $FEF_{25\%\text{-}75\%}$ are collected together with the spirometry assessments and will be presented in data listings only.
Rescue medication collected from eCRF and subject diaries will be will be presented in data listings only.

10.7 Safety Analyses

All safety analyses described below will be performed on the Safety population.

10.7.1 Adverse Events

As defined in the protocol, all AEs starting on or after the date of first study drug intake will be classified as TEAEs. Only TEAEs will be included in the tables. All AEs will be listed. AE onset date will be taken into account when assigning AEs as *treatment emergent*. Pre-treatment AEs (AE onset date < date of first randomized study drug intake) and post-study AEs (AE onset date > date of completion/discontinuation) will be included in the subject listings, and flagged, but will be excluded from other summaries.

The number of TEAEs, ADRs, serious TEAEs, serious ADRs, severe TEAEs, TEAEs leading to study drug discontinuation and TEAEs leading to death, and the number and the percentage of subjects experiencing TEAEs, ADRs, serious TEAEs, serious ADRs, severe TEAEs, TEAEs leading to study drug discontinuation and TEAEs leading to death will be summarized by treatment and overall.

The number and percentage of subjects with at least one AE and the number of AEs will be presented by SOC and PT by treatment and overall for treatment-emergent AEs, ADRs, serious TEAEs, serious ADRs, severe TEAEs, TEAEs leading to study drug discontinuation and TEAEs leading to death.

All available data will be considered in the summary of TEAEs: patients receiving a treatment twice will be considered twice in the corresponding treatment group (data from both periods during which the subject received the corresponding treatment will be included). Subjects who have multiple events in the same system organ class (SOC) and preferred term (PT) during a single treatment period will be counted only once in the subject counts for the corresponding treatment period. The number of subjects ("n"), the number of treatment periods ("n periods") and the number of events will be presented. Percentages will be based on the number of treatment periods in the Safety population.

10.7.2 Vital Signs

Vital signs (systolic and diastolic blood pressure) and their changes from baseline (pre-dose on Day 1) and from pre-dose on Day 14 (only for Day 14 post-dose time points) will be summarized by treatment using descriptive statistics and the 95% CI of the mean.
Mean absolute Vital signs (systolic and diastolic blood pressure) and their changes from baseline (pre-dose on Day 1) will be plotted for each of the treatment groups at Day 1 and Day 14.
For patients receiving the same treatment in 2 periods, each subject will contribute once to the summary statistics. Since 2 data points will be available, but the subject should only contribute once, the 2 available data points will be averaged for these subjects prior to calculation of the summary statistics for all subjects. In addition to the summary statistics also the number of treatment periods considered (“n periods”) will be reported.

10.7.3 ECGs

For continuous ECGs parameters, in case of patients receiving the same treatment in 2 periods, each subject will contribute once to the summary statistics. Since 2 data points will be available, but the subject should only contribute once, the 2 available data points will be averaged for these subjects prior to calculation of the summary statistics for all subjects. In

addition to the summary statistics also the number of treatment periods considered ("n periods") will be reported.

ECG parameters (HR, QTcF, QRS, and PR) at each time point will be summarized on Day 1 and Day 14 by treatment using descriptive statistics and the 95% CI of the mean. In addition, their changes from baseline and the changes from pre-dose on Day 14 (only for Day 14 post-dose time points) will be summarized using descriptive statistics and 90% CI.

In addition, the number and percentage of subjects with prolonged QTcF at any planned post dose time point will be summarized by treatment using counts and percentages on Day 1 and Day 14 Patients receiving a treatment twice will contribute only once to the summary statistics, using the highest QTcF value. The following thresholds will be used:

- QTcF >450 ms for males and >470 ms for females
- QTcF >480 ms for males only
- QTcF >500 ms
- Change from baseline in QTcF >30 ms and Change from baseline in QTcF >60 ms

For post-dose time-points on Day 14:

- change from pre-dose on Day 14 in QTcF >30ms and>60ms

At each post-dose time-point at Day 1 and Day 14, the change from baseline (pre-dose measurement on Day 1 of each Treatment Period) in 12-lead ECG parameters (HR, QTcF, QRS and PR) will be analyzed using an ANCOVA as stated in section 8.3. The adjusted means in each treatment group with their corresponding 90% CIs, and the adjusted mean difference between treatments with their corresponding 90% CIs will be estimated by the model. In addition, the p-values for each of the factors in the model will be displayed.

Mean absolute ECG parameters (HR, QTcF, QRS, and PR) at each time point and the mean change from baseline (pre-dose measurement on Day 1) at each time point will be plotted for each of the treatment groups at Day 1 and Day 14. These figures will be based on data from subjects in ITT population.

HR $AUC_{0\text{-}4h}$ normalized by time and HR $peak_{0\text{-}4h}$ on Day 1 and Day 14 and their changes from baseline (pre-dose measurement on Day 1 of each Treatment Period) and from pre-dose on Day 14 will be summarized by treatment using descriptive statistics and the CI of the mean (95% CI for absolute values and 90% CI for the changes from baseline/pre-dose).

12-lead ECG Abnormalities will be presented in data listings only.

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

- patients with a pacemaker already in place at study entry, identified by the presence of at least one of the following Preferred Terms in the medical/surgical history or concomitant diseases: "Cardiac pacemaker battery replacement", "Cardiac pacemaker evaluation", "Cardiac pacemaker insertion", "Cardiac

pacemaker replacement", "Electrocardiogram pacemaker spike", "Pacemaker generated arrhythmia", "Pacemaker generated rhythm", "Pacemaker syndrome", "Cardiac assistance device user";

- patients with a pacemaker implanted during the study, identified by a procedure coded with the Preferred Term "Cardiac pacemaker insertion" (other relevant cases may be identified in the Data Review Report). In this case, only the parameters assessed in a date ≥ start date of the procedure will be excluded from the statistical analysis;
- patients with atrial fibrillation as concomitant disease, identified by the presence of at least one of the following Preferred Term: "Atrial fibrillation", "Cardiac fibrillation", "Atrial flutter".
- ECGs with PR=0, since this is indicative of poor quality or inevaluble ECG result. Note that this does not apply to all ECGs for the patient, but only the ECGs with PR=0.

10.7.4 Clinical Laboratory Evaluation

Serum potassium and blood glucose at each time point and their changes from baseline (pre-dose measurement on Day 1 of each Treatment Period) and from pre-dose on Day 14 will be summarized by treatment using descriptive statistics and the 95% CI of the mean.

Mean absolute Serum potassium and blood glucose at each time point and their changes from baseline (pre-dose on Day 1) will be plotted for each of the treatment groups at Day 1 and Day 14 based on Safety population.

For patients receiving the same treatment in 2 periods, each subject will contribute once to the summary statistics. Since 2 data points will be available, but the subject should only contribute once, the 2 available data points will be averaged for these subjects prior to calculation of the summary statistics for all subjects. In addition to the summary statistics also the number of treatment periods considered ("n periods") will be reported.

In addition, all laboratory data will be listed, with abnormal values flagged.

10.8 Early Termination and Unscheduled Visits

The handling of the early termination efficacy and safety assessments in the statistical analyses will be discussed during the Data Review Meeting and the decisions will be fully documented in the Data Review Report.

With regards to unscheduled assessments, these measurements will be evaluated case by case during the Data Review Meeting, with handling described in the Data Review Report.

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

- Data collected at Day 1 and Day 14 of each period (spirometry, vital signs, serum potassium/glucose, and ECG) which is recorded at the study termination visit for discontinued patients will be re-allocated to the Day 14 visit of the same period. If the study termination visit was performed less than 7 days after the preceding visit, then the data recorded at the study termination visit will **not** be re-allocated and they will excluded from the statistical analysis.

- Additional unscheduled/optional spirometries will be considered on a case-by-case basis and their inclusion in the analysis will be discussed at the DRM and confirmed in the DRR prior to data base lock and unblinding. As a general rule, unscheduled or optional FEV_1 and FVC results which are recorded during the 12 hours post-dose at Visit 2 and Visit 4 will be considered in the $AUC_{0\text{-}12h}$ calculations, while results which are recorded during the 4 hours post-dose at Visit 2 and Visit 4 will be considered in the $AUC_{0\text{-}4h}$ and $peak_{0\text{-}4h}$ calculations and as eligible for minimum/maximum assessments unless otherwise specified in the DRR.

- Laboratories: the last assessment before the 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 first study drug intake will be considered in the analysis. If no complete assessment is available, the last assessment before first study drug intake with the highest number of available parameters 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.

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