CHIESI

BEAM

A 8-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO AND ACTIVE-CONTROLLED, PARALLEL GROUP, DOSE RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF 3 DOSES OF CHF 718 PMDI (BECLOMETHASONE DIPROPIONATE) IN ASTHMATIC SUBJECTS

Protocol: CCD-05993AA3-01

IND No: 133679

NCT no. NCT03084718

Statistical Analysis Plan

Version 1.0

Final

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Author:

[redacted]

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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

Abbreviation	Description
ACQ	Asthma Control Questionnaire
ADAM	Analysis Data Model
ADR	Adverse Drug Reaction
AE	Adverse Event
BID	Bis in die (twice a day)
BMI	Body Mass Index
BDP	Beclomethasone dipropionate
CDISC	Clinical Data Interchange Standards Consortium
Cm	Centimeters
CRF	Cases Report Form
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
ECG	ElectroCardioGram
eCRF	Electronic Case Report Form
E-RS	EXACT-Respiratory Symptom
FEV_1	Forced Expiratory Volume in the 1^{st} second
FVC	Forced Vital Capacity
H	Hours
HR	Heart Rate
IC	Inspiratory Capacity
ICS	Inhaled Corticosteroid
IRT	Interactive Response Technology
ITT	Intention-to-Treat (analysis population)
Kg	Kilograms
L	Liters
LABA	Long-Acting β_2-adrenergic receptor Agonist
LAMA	Long Acting Muscarinic Antagonist
µg	Micrograms
M	Meters
ms	Milliseconds
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
mL	Milliliter
PEF	Peak Expiratory Flow
pMDI	Pressurized Metered Dose Inhaler
PP	Per-Protocol (analysis population)
PR	PR Interval width (ECG)
PT	Preferred Term (MedDRA)
QC	Quality Control
Qd	Once a day
QRS	QRS interval width (ECG)
QTcF	QT interval width corrected according to Fridericia (ECG)
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SDTM	Study Data Tabulation Model
SOC	System Organ Class (MedDRA)
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization
WHO-DRL	World Health Organization – Drug Reference List

3 Protocol / Clinical Investigation Plan

This document presents the statistical analysis plan (SAP) for Chiesi Farmaceutici S.p.A., Protocol No. CCD-05993AA3-01: A 8-week, randomized, double-blind, placebo and active-controlled, parallel group, dose ranging study to evaluate the efficacy and safety of 3 doses of CHF 718 pMDI (beclomethasone dipropionate) in asthmatic subjects. This analysis plan is based on the final protocol (version 3.0) dated 19 OCT 2017 and the final electronic case report form (eCRF) (version 3.0) dated 26 OCT 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. In case of deviations from the SAP, explanations will be provided in the Clinical Study Report (CSR).

3.1 Study Objectives

The primary objective of this clinical trial is

- *To evaluate the efficacy of CHF 718 pMDI by comparison with placebo in terms of change from baseline in pre-dose morning FEV_1 at Week 8.*

There are 2 secondary objectives:

- *To evaluate the effect of CHF 718 pMDI on other lung function parameters and clinical outcome measures.*
- *To assess the safety and the tolerability of the study drug.*

3.2 Study Design

This is a phase II, multi-center, randomized, double-blind, placebo and active-controlled, parallel group, dose ranging study to evaluate the efficacy and safety of 3 doses of CHF 718 pMDI (HFA beclomethasone dipropionate) in adult subjects with asthma. Following a 2-week run-in period on ICS monotherapy, eligible subjects will be randomized to one of five study drugs (1:1:1:1:1) delivered twice-daily for 8 weeks. After the last assessment a follow-up phone call will be scheduled with the subject. The study will last approximately 12 weeks for each subject and a total of 5 clinic visits will be performed during the study. Subject will be randomized into 1 to 5 treatment groups presented below.

- Treatment A*: BDP 100µg Total Daily Dose (BDP 50µg per inhalation, 1 inhalation bid)
- Treatment B*: BDP 400µg Total Daily Dose (BDP 100µg per inhalation, 2 inhalation bid)
- Treatment C: BDP 800µg Total Daily Dose (BDP 100µg per inhalation, 4 inhalations bid)
- Treatment D: Matched placebo (4 inhalations bid)
- Treatment E: QVAR® 320µg Total Daily Dose (HFA beclomethasone dipropionate 80µg per ihhalation, 2 inhalations bid)

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

Background Medication for the Run-in Period

At the screening visit (Visit 1), treatments that are disallowed by the protocol are to be discontinued, including current ICS (as monotherapy or as combination ICS/LABA). The subjects will be instead prescribed an equivalent daily dose of ICS as beclomethasone dipropionate (QVAR® 40 or 80µg/actuation) and this treatment regimen should remain stable for the entire run-in period.

3.3 Study Schedule

	Pre-Screening	Screening	Treatment period			Follow-Up	ET
Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	
Time (Weeks)		-2	0	4	8	9	Early Termination
Window (days)			±2	±2	±2	±2	
Informed consent form	✓						
Demographic data	✓						
IRT visit confirmation call	✓	✓	✓	✓	✓	✓	✓
Inclusion / exclusion criteria		✓					
Asthma Action Plan Review		✓	✓	✓			
Eligibility recheck			✓				
Medical history/Previous medication		✓					
Weight, Height and BMI		✓					
Physical examination		✓	✓	✓	✓		✓
Hematology and Blood Chemistry		✓			✓		✓
Morning serum cortisol assessment		✓			✓		
Dispensing Container for 24-h Urine Collection[d]		✓		✓			
Collecting container for 24-h UFC & creatinine analysis[d]			✓		✓		
Serum pregnancy test [a]		✓			✓		✓
Urinary pregnancy test [a]		✓	✓	✓			
12-lead ECG[f]		✓	✓		✓		✓
Vital signs (SBP/DBP)[e]		✓	✓	✓	✓		✓
Spirometry pre and post-bronchodilator [b]		✓					
Pre-dose spirometry [c]			✓	✓	✓		✓
ACQ questionnaire		✓	✓	✓	✓		✓
Concomitant medications		✓	✓	✓	✓	✓	✓
Adverse Events assessment		✓	✓	✓	✓	✓	✓
Training on use of pMDI, e-diary and PEF meter		✓	✓				
e-diary, PEF meter completion		**✓ (daily)**					
Dispensation (D) / Return (R) of run-in QVAR®		D	R				R
Dispensation of rescue albuterol[g]		✓	✓	✓			
Study Drug dispensation(D)/ return & Accountability (R)			D	D/R	R		R

Subject diary dispensation (D) /return (R)		D	D/R	D/R	R		R

[a] In female subjects of childbearing potential only

[b] Spirometry will be carried out before and within 30 minutes after the inhalation of 4 puffs of albuterol to establish airway reversibility, if no documentation is available within 1 yr prior to V1.
[c] Pre-dose FEV_1, FVC: T -45' and T -15' before study drug administration at V2, V3, V4 and Early Termination at approximately the same time as done on V2.
[d] At V1, eligible subjects will be provided with a container for the 24-h urine collection, to be returned to the site the day after completing the collection, 1-2 days before or on the date of V2. At V3, subjects will be provided with a container for the 24-h urine collection, to be returned to the site after completing the collection, 1-2 days before or on the date of V4.
[e] Vital signs (SBP/DBP) will be measured at each visit, before the spirometry, bronchodilator, run-in ICS medication (QVAR®) or study drug intake.
[f] A 12-lead ECG will be measured at V1, V2 and V4 or Early Termination before the spirometry, bronchodilator, run-in ICS medication (QVAR®) or study drug intake.
[g] One commercial albuterol HFA MDI (200 actuations) will be prescribed and supplied by the investigator to each subject at V1, and resupplied as needed At V2-3 based on assessment of doses used between visits.

3.4 Randomization

A balanced block randomization scheme stratified by US Region (based on US Census Bureau Regions: West, Midwest, South, Northeast) and ICS dose before study (low/medium daily dose) will be prepared via a computerized system. Subjects will be centrally assigned to one of the five treatment arms at the end of the run-in period through an IRT system (Interactive Response Technology) with a 1:1:1:1:1 ratio.

The IRT will allocate the subject to a certain treatment group using a list-based randomization algorithm and will assign the study drug kit number corresponding to the treatment group assigned to the subject. The IRT will also generate a confirmation after every IRT transaction is performed.

The Investigator will call the IRT at each visit (from pre-screening to follow-up call) to record the subject number at pre-screening, to enroll and randomize the subject, to obtain the medication kit numbers and to register the subject status in the system. Detailed instructions for use of IRT will be provided to the site.

3.5 Sample Size Calculation

The sample size has been calculated to evaluate the superiority of CHF 718 pMDI at different doses over placebo in terms of change from baseline in pre-dose morning FEV_1 at Week 8.

A total of 495 evaluable subjects (99 per group) will provide 80% power to detect a mean difference of 200mL between each dose of CHF 718 pMDI and placebo at a two-sided significance level of 0.0167, assuming a standard deviation of 430mL.

Since three 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 (0.0167 = 0.05/3). 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 585 subjects (117 per group) will be randomized.

3.6 Efficacy and Safety Variables

Primary Efficacy Variable

Change from baseline in pre-dose morning FEV_1 (average of pre-dose FEV_1 measurements) at Week 8.

Secondary Efficacy Variables

Secondary Efficacy Variables are:

- *Change from baseline in pre-dose morning FEV_1 (average of pre-dose FEV_1 measurements) at Week 4*
- *Change from baseline in pre-dose morning FVC (average of pre-dose FVC measurements) at Week 4 and Week 8*
- *Change from baseline in ACQ-7 score at Week 4 and Week 8*

- *Change from baseline in average use of rescue medication during inter-visit periods and entire treatment period*
- *Change from baseline in percentage of rescue medication-free days during inter-visit periods and entire treatment period*
- *Change from baseline in daily asthma symptoms scores during inter-visit periods and entire treatment period*
- *Change from baseline in percentage of asthma symptoms-free days during inter-visit periods and entire treatment period*
- *Change from baseline in percentage of asthma control days during inter-visit periods and entire treatment period*
- *Change from baseline in morning and evening pre-dose PEF during inter-visit periods and entire treatment period*

Safety Variable

The list of safety assessments are:

- *Adverse Events (AEs) and Adverse Drug Reactions (ADRs)*
- *Vital signs (systolic and diastolic blood pressure)*
- *12-lead ECG parameters (HR, QTcF, QRS, PR)*
- *Standard blood chemistry and hematology*
- *24-h Urinary Free Cortisol and Creatinine*

3.7 Interim Analyses

No interim analyses are planned for this clinical investigation.

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

No changes in conduct between the Statistical Analysis Plan (SAP) and the study protocol have been noted.

4 General Definitions

4.1 Report Language

The output of the analyses (tables, figures, listings and inferential analysis) 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 22 JUN 2017) including the Data Validation Plan (Version 3.0 from 26 OCT 2017).

5.1.2 Coding

The following codes will be used 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 Reference List (WHO-DRL) 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. These third parties are:

- [redacted]: central laboratory data.
- [redacted]: drug intake details, PEF values, compliance values, spirometry data, rescue medication and Asthma Symptom Score results.
- [redacted]: supplies the randomization numbers and treatment codes 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, 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 primary efficacy analysis will be based on the ITT population. The primary efficacy analysis will be also performed on the PP populations for sensitivity purpose.

The secondary efficacy variables will be analyzed in the ITT population.

All 3 populations (Safety, ITT, and PP) will be used for the presentation of demographics, asthma history and smoking, and spirometry and reversibility.

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

Medications, compliance with the use of e-diary, and protocol deviations will be reported using the ITT population.

The safety data will be summarized and reported using the Safety population.

6.2 Treatment Misallocation

In case of deviation between the as-randomized treatment and the treatment actually received, the treatment 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 populations, given there will be no randomized treatment. These subjects will be summarized based on the treatment they received and will be counted in the Safety population.
- Subjects who were randomized, but took the incorrect study drug for the duration of the study, will be summarized based on their randomized treatment for the ITT population and excluded from the PP population. These subjects will be summarized based on the treatment that they received for the safety analyses.

- Subjects who were randomized, but took the incorrect study drug for part of the study (e.g. the subject began the study by taking the incorrect study drug at Visit 2 but switched to randomized study drug at Visit 3) will be discussed during the Blind Data Review Meeting, 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

Start/End of the Randomized Treatment Period

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

- The date of **Start of the Randomized Treatment Period** 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 4 or Early Termination visit was completed, then the date of **End of the Randomized Treatment Period** will be defined as Date of Visit 4/ Early Termination Visit. 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 during treatment period (excluding Visit 5 and any unscheduled visits after last dose)].

Period durations (days)

Day 1 is defined as the date of the first dose of randomized study drug. The day prior to Day 1 is Day -1. There is no Day 0.

Periods used in the analysis of this study are:

- Run-in Period: Morning of Visit 1 through the evening of the day before the date of Start of the Randomized Treatment Period.
  Run-in duration = date of the day before the date of the Start of the Randomized Treatment Period – date of Visit 1 + 1 day

- Treatment Period: (End of the Randomized Treatment Period minus Start of the Randomized Treatment Period) + 1 day

Inter-visit periods will be used in the analysis of the average number of rescue medication, the percentage of rescue medication-free days, the percentage of asthma symptoms-free days and of asthma control day, the daily asthma symptoms scores and the morning and evening average pre-dose PEF. The periods used in these analyses are:

- Run-in Period: The Run-In Period starts at Visit 1 and runs through morning assessment of the date of Start of the Randomized Treatment Period.

- Inter-visit Period 1: Inter-visit Period 1 starts on the evening assessment of the date of the Start of the Randomized Treatment Period and runs through the morning assessment on the date of Visit 3.If the subject withdraws prematurely after Visit 2 and before Visit 3 any value collected from Visit 2 until the End of the Randomized Treatment Period will be considered for the Inter-visit Period 1. By default Inter-visit Period 2 is missing.
- Inter-visit Period 2: Inter-visit Period 2 starts on the evening assessment of the day the subject returns to the clinic at Visit 3 and runs through the morning assessment of the date of Visit 4.

  If the subject withdraws prematurely after Visit 3 and before Visit 4 any value collected from Visit 3 until the End of the Randomized Treatment Period will be considered for the Inter-visit Period 2.

Date of first/last study drug intake

Date of first randomized study drug intake is derived as the minimum of 'Date/Time of administration' between the 4 inhalations (puffs) of the Morning Dose collected on the 'Study drug administration at the clinic' eCRF page. While subjects randomized to open-label QVAR® will only receive 1 inhaler, patients are required to take 2 inhalations of the content of 1 inhaler on site, the morning of Visit 2. For these patients, no minimum is required, since only 1 time is recorded.

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 CRF data will be considered for the date of first randomized study drug intake.

Date of last randomized study drug intake is derived as 'Date/Time of last intake of study drug' variable collected on the 'Study Termination form' eCRF page. If the date of the 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/completion 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 for lost to follow up or early withdrawal. 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) / 7

Baseline definitions

Demographic data will be recorded during Visit 0 (Pre-Screening visit). All other baseline characteristics (medical history, concomitant diseases, previous and concomitant medications) will be recorded during Visit 1 (Screening).

For the primary efficacy endpoint, the baseline value is defined as the average of the FEV_1 pre-dose measurements on Visit 2 (45 min and 15 min pre-dose). In the same manner, for FVC the average of the FVC pre-dose measurements recorded at Visit 2 on Day 1 will be used as the baseline. *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 used in the analysis of PEF and diary data is the result recorded during the Run-in Period. Depending on the structure of the specific variable, this may be an average value, or a percentage.

Baseline ACQ-7 score is the ACQ score recorded at Visit 2, before randomization.

For vital signs, 12-lead ECG and urinary cortisol and creatinine, baseline values are those recorded pre-dose at Visit 2.

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

7.2 Baseline Characteristics 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 eCRF system based on the date of birth and date of Pre-Screening (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:
  (Visit 1 - 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 as: (smoking stop date - smoking start date + 1)/365.25

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 Screening and Baseline Subject Characteristics

- Asthma Control Questionnaire (ACQ) score at Visit 1 and Visit 2will be calculated within the eCRF.
- 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 collected at Visit 1 and calculated as Weight (kg) / [Height (m)]²
- Use of rescue medication, asthma symptoms, and PEF are collected twice daily during the run-in period via subject eDiary. For derivation of summary statistics for rescue medication, asthma symptoms, and PEF during the run-in period, a minimum of 7 days with some non-missing data is required.
- Spirometry will be performed prior to and following bronchodilator at Visit 1 and prior to dosing at Visit 2.

7.2.4 Spirometry and ACQ at Screening

At Visit 1, if documentation of airway reversibility within 1 year prior to V1 is not available, airway reversibility will be assessed with spirometry in triplicate maneuvers before and within 30 minutes after administration of 4 separate doses of albuterol HFA (90µg/actuation, total dose 360µg) at 30-sec intervals. The reversibility parameters (i.e., ΔFEV_1 (mL), % ΔFEV_1) will be calculated in the eCRF. Historical reversibility will be presented separately from reversibility calculated during the study.
If the reversibility test of Visit 1 is repeated in a (pre-randomization) rescheduled visit (called Visit 1.1 in the eCRF), then all spirometry values of the rescheduled visit will be used for the analysis. The same approach will be applied to ACQ.

7.2.5 Previous and Concomitant 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 and medication stop date ≤date of first study drug intake).
- **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 and medication stop date > date of first study drug intake).
- **Concomitant medications** are all medications started during the treatment period (date of first study drug intake <= medication start date < date of last study drug intake).

- **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).

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. post-treatment medication;
4. prior medication.

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

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

Common name	Preferred Names
"BUDESONIDE"	"BUDESONIDE"
"FLUTICASONE W/SALMETEROL"	"FLUTICASONE W/SALMETEROL" "SERETIDE" "FLUTICASONE PROPIONATE W/SALMETEROL"
"BUDESONIDE W/FORMOTEROL"	"BUDESONIDE W/FORMOTEROL" "BUDESONIDE W/FORMOTEROL FUMARATE"
"FLUTICASONE W/VILANTEROL"	"BREO ELLIPTA" "FLUTICASONE FUROATE W/VILANTEROL"
"MOMETASONE W/FORMOTEROL"	"DULERA"
"IPRATROPIUM W/SALBUTAMOL"	"COMBIVENT" "IPRATROPIUM W/SALBUTAMOL"

7.2.6 Previous and Concomitant Procedures

Procedures will be split into two categories:

- **Previous procedures** are all procedures started and stopped prior to the treatment period (procedures start date < date of first study drug intake and procedures stop date ≤ date of first study drug intake).

- **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 and procedures stop date > date of date of first study drug intake).
- **Concomitant procedures** are all procedures started during the treatment period (date of first study drug intake <= procedures start date < date of last study drug intake).
- **Post-treatment procedures** are all procedures started on or after the end of randomized period (procedures start date >= date of last study drug intake).

In case of missing or incomplete dates not directly allowing allocation to the any of 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. maintained procedures;
3. post-treatment procedures;
4. previous procedures.

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

7.2.7 Treatment Exposure and Compliance – Background Medication

Run-In Period / Exposure and Compliance

At Visit 1*, the investigator will prescribe the subject QVAR® 40µg or QVAR® 80µg 1-2 puffs bid (80 – 320µg/d) at an equipotent dose to replace the subject's prior ICS. The 1st dose of QVAR® will be administered on-site at V1. Subsequently, the subject will be instructed to discontinue the use of any other ICS for the duration of the study. The background QVAR® medication should not be taken in the morning before coming to the clinic (at V1.1 and V2) and will be discontinued at V2.* This treatment regimen should remain stable for the entire run-in period.

The Run-In Period starts at Visit 1 and runs through the day before Day 1 (Day -1). Note that the morning diary questions refer to the previous evening. Therefore, assessments related to the evening of the day before Day 1 (Day -1) will be answered in the diary on the morning of Day 1. Exposure during the Run-in Period are based on actual dosing date/times and not visit dates. Exposure will be calculated using the:

date of last dose of the Run-in Period – date of first dose of the Run-in Period + 1 day.

Compliance to background medication during the run-in period is based on eCRF and diary data. If visit 1 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:

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

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 (days)] x [scheduled number of puffs per day]

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

The compliance will be summarized using the following categories:

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

and the 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%

7.2.8 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 for the 8-week treatment period; study drug will be administered twice-a-day (in the morning and in the evening), with the last dose taken the evening before Visit 4. Note that the morning diary questions refer to the previous evening. Therefore, assessments related to the evening of the day before Day 1 (Day -1) will be answered in the diary on the morning of Day 1.

For **Treatment Arms A, B, C and D** dosing schedule is:

<u>Morning administration (between 8-10 am):</u>

One inhalation from the canister labeled 1
One inhalation from the canister labeled 2
One inhalation from the canister labeled 3
One inhalation from the canister labeled 4

Evening administration (between 8-10 pm):

One inhalation from the canister labeled 1
One inhalation from the canister labeled 2
One inhalation from the canister labeled 3
One inhalation from the canister labeled 4

For **Treatment Arm E** dosing schedule is:

Morning administration (between 8-10 am):

Two inhalations from QVAR® 80 µg pMDI

Evening administration (between 8-10 pm):

Two inhalations from QVAR® 80 µg pMDI

If the settings in the electronic diary are incorrect at randomization for a subject (e.g., Run-in period settings are applied during the treatment period), such that data is not collected for study drug administration during some days during the treatment period, then compliance and exposure will not be calculated for that subject for sessions (morning/evening) on which the settings were incorrect. Instead, compliance will be calculated based on sessions during which the settings were correct. The information recorded at the study clinic will always be considered in the calculation (i.e. day will be considered in calculation if exposure is recorded at clinic in a day where diary has an incorrect setting). For these subjects, the duration of the treatment period (as used for calculation of scheduled puffs) will be reduced by the number of days during which the settings were incorrect. In other words, days with incorrect diary settings will be excluded from the numerator and denominator of the compliance calculation for these subjects. If the diary settings were incorrect during the entire treatment period, then compliance and exposure will not be calculated for the subject. To be considered as incorrect, diary data should be nonmissing and questions answered consistent with a different period. For example (I=incorrect questions, C=correct questions, M=missing data):

- Day 1: I
- Day 2: I
- Day 3: M
- Day 4: M
- Day 5: C.

In this case, the last "incorrect day" is Day 2.

The same approach will be applied to sessions for which any questions related to the wrong treatment arm (ABCD vs E) were asked, that will not be used in the calculation of compliance. Notably, these sessions will not contribute to the numerator (number of administered puffs) or the denominator (number of scheduled puffs). For these subjects, the total number of scheduled puffs will be based on treatment exposure days, excluding sessions with any incorrect diary questions. This includes sessions where duplicate questions were answered. In these cases, all data at the session is considered unreliable, so even the correct questions will be excluded.

The dosing occasions for study drug are expected to be taken during the visit dates, however exposure and compliance are 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 doses, the dosing occasions from the first to the last study drug intake will be taken into account (i.e. any study drug recorded in the Subject Diary after the date of last dose (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 until the 'last randomized study drug intake' as defined in Section 7.1.

Exposure will be calculated as the Date of last intake of study drug – date of first intake of study drug + 1 day.

The evaluation of compliance is done using the following formula:

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

The **total number of administered puffs** will be calculated by adding up the number of puffs taken during the Treatment period, as recorded in the Subject Diary and 'Study Drug Administration at the Clinic' eCRF page.

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

It should be noted that 4 puffs (for Arms A, B, C, and D) or 2 puffs (for Arm E) should be taken twice a day during the Treatment period (from the morning of Day 1 (V2) until the evening of the day before V4). No study treatment is to be administered on the morning of Visit 4.

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

The total number of scheduled puffs is defined during the treatment period as:

- 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].

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

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

The 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%

7.2.9 Compliance with the use of e-Diary

If the setting in the electronic diary are incorrect for a subject (e.g., Run-in settings applied during treatment period or vice-versa), then compliance with use of e-Diary will still be considered.

In these cases, if any questions were answered, the session will count as "data recorded in the [redacted] device".

Compliance with the use of e-Diary is based on visit dates. See Section 7.1 for the definition of the study periods and period durations (days). Period duration will be calculated differently for completed subjects and discontinued subjects as defined in Section 7.1.

Of note, the Visit 2 morning session relates to the run-in period, so this session is considered in the total number of sessions expected during the run-in.

The evaluation of compliance per period (Run-in/Treatment Period) is done using the following formula:

$$\frac{\text{Total number of sessions in the treatment period with data recorded in eDiary}}{\text{Total number of sessions expected per Period}} \; x \; 100\%$$

The following categories will be discerned for compliance:

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

- (80%-90%]
- (90%-100%]

7.2.10 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 calculation of the derived variables. This follows the approach recommended by the paper by Hankinson et al. (Eur Respir J 2015), where it was concluded that quality assessment regarding the acceptability of individual blows should be primarily used as an aid to 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 case of historical reversibility data are reported in eCRF only.

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 pre-dose morning FEV_1 at Week 8. 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]).

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.

In case of rescue medication intake on a visit day, all spirometry data recorded from the time of rescue medication intake onwards for 6 hours will be analyzed as part of the ITT Population with no exception, but they will be excluded from the analysis of primary efficacy endpoint for the PP population.

Secondary Efficacy Variables

In case of rescue medication intake on a visit day, all spirometry data recorded will be analyzed as part of the ITT Population with no exception.

For the derivations of secondary efficacy variables like, average use of rescue medication percentage of rescue medication-free days, daily asthma symptoms scores, number and percentage of asthma symptoms-free days, number and percentage of asthma control days, a minimum of 7 days with available measurements will be required for each inter-visit period (including the run-in period) to consider the variable as non-missing. For these variables, a

"day" is considered as the evening diary session (for which questions relate to the morning) and the following morning diary session (for which questions relate to the prior evening).

- *Change from baseline in pre-dose morning FEV_1 at Week 4*

FEV_1 is a continuous variable derived from spirometry data ([redacted]). The baseline value is the average of the T-45 and T-15 min pre-dose FEV_1 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.

- *Change from baseline in pre-dose morning FVC at Week 4 and Week 8*

FVC is a continuous variable derived from spirometry data ([redacted]). The baseline value is the average of the T-45 and T-15 min 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.

- *Change from baseline in ACQ-7 score at Week 4 and Week 8*

The ACQ consists of 7 items: six simple self-administered questions referring to asthma control and rescue treatment usage with one week recall, and a seventh item consisting of the % predicted FEV_1 completed by clinic staff. Scoring uses a 7-point scale, with 0 indicating "totally controlled" and 6 indicating "severely uncontrolled". The ACQ score will be calculated as the average of all 7 items.

ACQ mean score is recorded on 'Asthma Control Questionnaire" eCRF page. Baseline ACQ-7 score is the ACQ score recorded at Day 1, before randomization.

- *Change from baseline in average use of rescue medication (number of puffs/day) during inter-visit periods and entire treatment period*

Information on rescue medication use is collected in the subject- e-diary and in the eCRF at clinic. The change from baseline in the average use of rescue medication is a continuous variable. The average use of rescue medication is calculated as

$$\frac{\sum \text{Number of puffs of rescue medication taken}}{\text{Number of days with available data}}$$

In case of duplicates information reported at clinic and in diary, the greatest information will be used. The average use of rescue medication of the entire treatment period will be derived only if both inter-visit period are non-missing. See Section 7.1 for the definition of the inter-visit and entire treatment periods.
If only a single diary session is missing for a given day (evening session or morning session), then the non-missing session will be used. If both sessions are missing, the day will be considered as missing.

- *Change from baseline in percentage of rescue medication-free days during inter-visit periods and entire treatment period.*

Information on rescue medication use is collected in the subject-completed e-diary and in the eCRF at clinic. A patient is assumed to have used rescue medication if the answer to either of the following questions is >0:

- How many times did you take rescue medication during the nighttime/daytime?
- How many inhalations of rescue medication did you take during the nighttime/daytime?

In case of duplicates information reported at clinic and in diary, the greatest information will be used. The change from baseline in the percentage of rescue medication-free days is a continuous variable. The percentage of rescue medication-free days is calculated as

$$\frac{\text{Number of rescue medication} - \text{free days}}{\text{Number of days with available data}} x100\%$$

The percentage of rescue medication-free days during the entire treatment period will be derived only if both inter-visit period are non-missing. See Section 7.1 for the definition of the inter-visit and entire treatment periods.

If only a single diary session is missing for a given day (evening session or morning session), then the non-missing session will be used. If both sessions are missing, the day will be considered as missing.

- *Change from baseline in daily asthma symptoms scores during inter-visit periods and entire treatment period*

The change from baseline in daily asthma symptoms score is a continuous variable. Subjects have to record asthma symptom score (overall symptoms, cough, wheeze, chest tightness and breathlessness) in the morning (night-time asthma symptom score) and in the evening (daytime asthma symptom score). These data are collected on the subject's diary.

Daily asthma symptoms score are performed separately for morning score and evening score and also as a total, where the total equal the sum of the morning and evening scores.

The daily morning asthma symptoms score is calculate as

$$\frac{\sum \text{Daily Asthma Symptoms score } (morning)}{\text{Number of days with available data}}$$

where "Daily Asthma Symptoms scores (morning)" is considered separately for "Cough", "Wheeze", "Chest Tightness", "Breathlessness" and "overall symptoms" morning individual scores.

Degree of each asthma symptoms is evaluated using a 4-point scale from 0 to 3: None (0), Mild (1), Moderate (2) and Severe (3).

Daily asthma symptoms score during the entire treatment period will be derived only if both inter-visit period are non-missing. See Section 7.1 for the definition of the inter-visit and entire treatment periods.

The daily evening asthma symptom score will be computed as defined for morning score using evening individual symptom scores.

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

For each day of the treatment period, for each symptom, the "daily symptom score" will be calculated as the mean of the evening symptom score of the day and morning symptoms score of the next day.

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

- *Change from baseline in percentage of asthma symptoms-free days during inter-visit periods and entire treatment period*

The change from baseline in the percentage of asthma symptoms-free days is a continuous variable. The percentage of asthma symptoms-free days is calculated as

$$\frac{\text{Number of asthma symptoms} - \text{free days}}{\text{Number of days with available data}} x100\%$$

Asthma symptoms-free days is the number of days with a total asthma score = 0 (daily morning plus evening asthma score).

If only a single diary session is missing for a given day (evening session or morning session), then the non-missing session will be used. If both sessions are missing, the day will be considered as missing. The percentage of asthma symptoms-free days during the entire treatment period will be derived only if both inter-visit period are non-missing. See Section 7.1 for the definition of the inter-visit and entire treatment periods.

- *Change from baseline in percentage of asthma control days during inter-visit periods and entire treatment period*

The change from baseline in percentage of asthma control day is a continuous variable. The percentage of asthma control day is calculated as

$$\frac{\text{Number of asthma control days}}{\text{Number of days with available data}} x100\%$$

The derived variable of Asthma Control Days will be calculated according to the following definition:

Days with a total daily morning + evening asthma score = 0

AND no rescue medication use.

If only a single diary session is missing for a given day (evening session or morning session), then the non-missing session will be used. If both sessions are missing, the day will be considered as missing. The percentage of asthma control days -free days during the entire treatment period will be derived only if both inter-visit period are non-missing. See Section 7.1 for the definition of the inter-visit and entire treatment periods.

- *Change from baseline in morning and evening pre-dose PEF during inter-visit periods and entire treatment period*

PEF measurement is a continuous variable derived from an electronic peak flow meter. During each measurement session (morning or evening before the intake of the run-in ICS medication or study drug) the subject will perform 3 exhalations. Data will be recorded in the [redacted] device (e-diary). For analysis, the derived PEF to be used will be the highest value of the available PEF measurements for the given time point.

A minimum of 2 PEF values should be available at a given time point in order to calculate the derived PEF for analysis. Otherwise, if fewer than 2 PEF values are available for a given time point, that time point will be considered as missing for analysis of PEF. A minimum of 7 days with available measurements will be required for each inter-visit period (including the run-in period) to consider the morning and evening pre-dose PEF as non-missing. The morning and evening pre-dose PEF during the entire treatment period will be derived only if both inter-visit period are non-missing. See Section 7.1 for the definition of the inter-visit and entire treatment periods.

7.2.11 Safety Assessments

There are 5 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 before the first randomized study medication intake (AE onset date < date of first randomized study medication intake).
- 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 ≤ 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).

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 + 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. Relative day will not be calculated in case of partial/missing date of AE onset.
- *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 date – AE onset date + 1 and the duration will be reported as ">x" in the listing. 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)

Vital signs (systolic and diastolic blood pressure) will be measured pre-dose from Visit 1 to Visit 4. Blood pressure measurements are continuous variables and recorded in mmHg. Change from baseline will be calculated using the pre-dose assessment on Day 1 as the baseline value.

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

The following parameters from 12-lead ECG will be measured at Visits 1, 2 and 4 and at the Early Termination visit:

- Heart rate (HR) (bpm);
- PR interval (msec)
- QRS interval (msec)
- QTcF interval (msec).

QTc value will be calculated using the Friderica formula (Fridericia-corrected QTc=$\frac{QT}{\sqrt[3]{RR}}$) It will be calculated automatically by the ECG recorder.

The changes from baseline will be based on the pre-dose assessment on Day 1.

- 4: Standard blood chemistry and hematology

Blood samples will be collected for hematology and serum chemistry at Screening and Week 8. Blood samples will also be collected at Early Termination in the morning.

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).*
- *Fasting blood glucose*
- *Serum pregnancy test (serum β-hCG) in women of child-bearing potential;* results will be presented as positive or negative. Urine β-hCG from visits 1, 2, and 3 will also 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.

- 5: 24-h Urinary Free Cortisol and Creatinine

24-hour urine sample will be collected at Visit 2 and at Visit 4 for the measurement of urinary free cortisol and creatinine excretion.

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.

For **continuous variables**, summary statistics will include the number of non-missing observations, 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.

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.

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):

- BMI, treatment exposure (days): whole numbers;
- Time to discontinuation (weeks), duration of smoking (years), time since first asthma diagnosis (years), compliance, average use of rescue medication (number of puffs/day), percentage of rescue medication-free days, asthma symptoms scores, percentage of asthma symptoms-free days, percentage of asthma control days: 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;

- 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 document. SAS output results will be delivered only after DB lock.

Calculation of adjusted means (least squares means):

The approach described below will ensure that the least squares means calculated by SAS will be based on:

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

The analysis is based on the following steps:

1. generate a dataset by selecting:
   - in case of repeated post-randomisation measurements (e.g., FEV_1 at each visit, analysed using a linear mixed model for repeated measures): all the post-randomisation records for subjects with at least one available and valid post-randomisation measurement and no missing covariates;
2. in case of repeated post-randomisation measurements, add to the dataset generated in step 1 the records for missing post-randomisation visits of the subjects included in the dataset. In the added records the value of the response variable will be missing, but the full information on covariates has to be included;
3. use the dataset obtained as the input dataset for the MIXED procedure, specifying the following options in the LSMEANS statement:
   - in case of repeated post-randomisation measurements: OM AT MEANS;

Example: analysis of change from baseline (Visit 2) at all visits (Visits 3 to 5) based on a mixed model for repeated measures including the effects of treatment, visit (categorical variable), treatment by visit interaction, baseline and another covariate. Visit 1 represents the screening visit.

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

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

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

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

Step 2 (added records in *italic*):

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

8.1.1 Rules for Handling Missing Data

Handling of missing data for the statistical analysis is described below:

For the primary efficacy analysis, a linear mixed model for repeated measures will be used to handle missing data. Under the Missing At Random (MAR) assumption, this model provides an unbiased estimate of the treatment effect that would have been observed if all subjects had continued on treatment for the full study duration. This approach addresses efficacy (or de jure) hypotheses, estimating the causal effects of the initially randomized drug if taken as directed (in contrast with effectiveness, or de facto, hypotheses, evaluating the effect of the drug as actually taken). The efficacy estimand is considered appropriate in the context of a phase II study aiming at characterizing dose-response.

The specific ways how to deal with missing data, in particular with partial or missing dates (e.g., of medication use), missing spirometry data and missing questionnaire data, is 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

● Primary Model for Analysis

The change from baseline in pre-dose morning FEV_1 at week 8 will be analyzed using a linear mixed model for repeated measurements including treatment, visit, treatment by visit interaction, ICS dose before study (low/medium daily dose) and US regions as fixed effects, and the baseline value (average of the pre-dose FEV_1 measurements on Day 1) and baseline by visit interaction as covariates. An unstructured covariance matrix will be assumed; the generic code for the model is presented below.

```
proc mixed data = <xxx>;
 class subject treatment visit usregion ICSdose;
 model <response> = treatment  visit  treatment*visit  usregion ICSdose fev1base fev1base*visit / DDFM=KR;
 repeated  visit / subject=subject  type=UN;
 lsmeans treatment*visit / cl OM AT MEANS;
 lsmestimate treatment*visit 'Trt A vs Placebo week 8' 0 1 0 0 0 0 0 -1 0 0,
                'Trt B vs Placebo week 8' 0 0 0 1 0 0 0 -1 0 0,
                'Trt C vs Placebo week 8' 0 0 0 0 0 1 0 -1 0 0 / cl adjust=simulate (seed=12311980 acc=0.0001);
 lsmestimate treatment*visit  'Trt B vs Trt A week 8' 0 -1 0 1 0 0 0 0 0 0 /cl;
 lsmestimate treatment*visit 'Trt C vs Trt A week 8' 0 -1 0 0 0 1 0 0 0 0 /cl;
 lsmestimate treatment*visit 'Trt C vs Trt B week 8' 0 0 0 -1 0 1 0 0 0 0 /cl;
 lsmestimate treatment*visit  'Trt E vs Placebo week 8' 0 0 0 0 0 0 0 -1 0 1 /cl;

run;
```

where:

- *treatment* is the randomized treatment variable, codified and sorted as follow:
    1. Treatment A (BDP 100µg)
    2. Treatment B (BDP 400µg)
    3. Treatment C (BDP 800µg)
    4. Placebo
    5. Treatment E (QVAR 320 µg)
- *visit* is the visit variable (Visit 3 [week 4] and Visit 4 [week 8])
- *treatment*visit* is the treatment by visit interaction
- *usregion* is the region in the United States from which the subject entered the study (Midwest, Northeast, South and West Regions).
- *ICSdose* is the ICS dose before the study (low/medium daily dose)
- *fev1base* is the baseline FEV_1 result
- *fev1base*visit* is the baseline FEV_1 result by visit interaction.

The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% Confidence Intervals (CIs) will be estimated by the model. The CIs and the p-values of the comparisons between each dose of CHF 718 pMDI and placebo at Week 8 will be adjusted for multiplicity. For the primary endpoint, 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 718 pMDI will be demonstrated by a **statistically significant** difference (adjusted p-value < 0.05) favoring CHF 718 pMDI.

The model will include also pairwise comparisons of treatment A through treatment C, comparing each dose with a lower dose, and treatment E versus Placebo. The CIs and the p-values of these comparisons at Week 8 will not be adjusted for multiplicity.

Kenward Roger's method will be used to approximate denominator degrees of freedom (/DDFM=KR in the MODEL statement); OM and AT MEANS in LSMEANS statement will be used to account for unbalanced population (see details in 8.1).

Sensitivity analysis:

Primary analysis will be repeated for sensitivity analysis considering the ICS dose as reported in the IVRS system at randomization.

Another sensitivity analysis, exactly as the primary analysis, will be repeated incorporating only the spirometry with Grade="Acceptable".

Secondary efficacy endpoints

For the secondary efficacy analyses (pre-dose morning FEV_1 at Week 4, pre-dose morning FVC at Week 4 and Week 8, ACQ-7 score at Week 4 and Week 8, average use of rescue medication, percentage of rescue medication-free days, daily asthma symptoms scores, percentage of asthma symptoms-free days, percentage of asthma control days, morning and evening pre-dose PEF) the same model as above defined for the primary efficacy variable will be used with no multiplicity adjustment.

The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% Confidence Intervals (CIs) will be estimated by the model. The CIs and the p-values of the comparisons between treatments at Week 4 or Week 8 will not be adjusted for multiplicity.

For analysis of use of rescue medication, rescue-medication free days, daily asthma symptoms scores, asthma symptoms-free days, asthma control days, morning and evening pre-dose PEF the inter-visit period will be considered instead of visit in the model. Comparison between treatments over the entire treatment period will also be derived from this model. The generic code for the model is presented below.

```
proc mixed data = <xxx>;
 class subject treatment inter_visit usregion ICSdose;
 model <response> = treatment inter_visit treatment*inter_visit usregion ICSdose base base*inter_visit /
  DDFM=KR;
 repeated inter_visit / subject=subject type=UN;
 lsmeans treatment treatment*inter_visit / cl OM AT MEANS;
 lsmestimate treatment "Trt A vs Placebo entire tmt period" 1 0 0 -1 0 /cl;
 lsmestimate treatment "Trt B vs Placebo entire tmt period" 0 1 0 -1 0 /cl;
 lsmestimate treatment "Trt C vs Placebo entire tmt period" 0 0 1 -1 0 /cl;
 lsmestimate treatment "Trt B vs Trt A entire tmt period" -1 1 0 0 0 /cl;
 lsmestimate treatment "Trt C vs Trt A entire tmt period" -1 0 1 0 0 /cl;
 lsmestimate treatment "Trt C vs Trt B entire tmt period" 0 -1 1 0 0 /cl;
 lsmestimate treatment "Trt E vs Placebo entire tmt period" 0 0 0 -1 1 /cl;
 lsmestimate treatment*inter_visit 'Trt A vs Placebo period 1' 1 0 0 0 0 0 -1 0 0 0 /cl;
 lsmestimate treatment*inter_visit 'Trt B vs Placebo period 1' 0 0 1 0 0 0 -1 0 0 0 /cl;
 lsmestimate treatment* inter_visit 'Trt C vs Placebo period 1' 0 0 0 0 1 0 -1 0 0 0 /cl;
 lsmestimate treatment* inter_visit 'Trt B vs Trt A period 1' -1 0 1 0 0 0 0 0 0 0 /cl;
 lsmestimate treatment* inter_visit 'Trt C vs Trt A period 1' -1 0 0 0 1 0 0 0 0 0 /cl;
 lsmestimate treatment* inter_visit 'Trt C vs Trt B period 1' 0 0 -1 0 1 0 0 0 0 0 /cl;
 lsmestimate treatment* inter_visit 'Trt E vs Placebo period 1' 0 0 0 0 0 0 -1 0 1 0 /cl;
lsmestimate treatment* inter_visit "Trt A vs Placebo period 2" 0 1 0 0 0 0 0 -1 0 0 /cl;
…
 lsmestimate treatment* inter_visit "Trt E vs Placebo period 2" 0 0 0 0 0 0 0 -1 0 1 /cl;
run;
```

8.2.1 Statistical/Analytical Issues

8.2.1.1 Handling of Dropouts or Missing Data

The rules to address missing data rules for specific variables are described in Section 7.2 and 8.1.1.

8.2.1.2 Blind Review

A Blind Data Review Meeting is organized just before database 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 which cannot be resolved prior to database lock. The Data Review Plan will describe the tables, listings and figures used during this meeting, and falls outside the scope of the SAP.

8.2.1.3 Multi-center Studies

No adjustment is done for the multiple centers, and no analysis per center is carried out. The adjustment in the model will be US region.

8.2.1.4 Multiple Comparisons/Multiplicity

Adjustment for multiplicity is applicable only to the primary efficacy analysis. The CIs and the p-values of the comparisons between each dose of CHF 718 pMDI and placebo for the primary efficacy endpoint at Week 8 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 718 pMDI will be demonstrated by a **statistically significant** difference (adjusted p-value < 0.05) favoring CHF 718p MDI.

8.2.1.5 Patients Randomized to Incorrect Inhaled Corticosteroid Dose Stratum

If, during randomization, a patient was incorrectly randomized to the wrong stratum for Inhaled Corticosteroid Dose, then the patient will be analysed as if he/she had been assigned to the correct stratum. For example, Subject was stratified to MEDIUM ICS stratum. According to the ICS dosage taken before the study entry the correct stratum was LOW. Subject will be analysed as if he/she had been assigned to the LOW stratum.

9 Interim analyses

Not applicable.

10 Overview of Tables, Listings and Figures

Demographics, asthma and smoking history, 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, efficacy variables derived from diary data, compliance use of e-diary, compliance with background medication and protocol deviations will be presented using the ITT population. vital signs, ECG, AEs and laboratory data will be presented using the Safety population.

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 by treatment and overall 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 will be also summarized by treatment using absolute counts and percentages, based on the number of subjects randomized. A Kaplan Meier plot will be reported by treatment.

10.2 Protocol Deviations

The number of subjects who had at least one Major Protocol Deviation and all Major Protocol Deviations will be summarized by absolute counts (n) and percentages (%) by treatment for the ITT population. Percentages will be based on the number of subjects in the ITT population. The summary will be repeated for Major and Minor Protocol Deviations.

10.3 Data Sets to be Analyzed

The number of subjects in each population will be summarized by treatment and overall, by absolute counts (n) and percentages (%) for each treatment group. Percentages will be based on the number of randomized subjects. The summary will be repeated by treatment and regions.

10.4 Demographic and Other Baseline Characteristics

10.4.1 Demographic Characteristics

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

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 (%) by treatment and overall 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.

10.4.3 Screening and Baseline Subject Characteristics

Central spirometry and reversibility test data, Vital signs, ECG results, and Asthma Control Questionnaire at Visit 1 and Visit 2 will be summarized with summary statistics and absolute counts (n) and percentages (%) by treatment and overall for populations as described in Section 6 above.

Reversibility test data will be presented overall and also separately for reversibility calculated during the study and historical reversibility.

Use of rescue medication, asthma symptoms, asthma control days, and PEF during the run-in period will be presented using summary statistics. For these summaries, a minimum of 7 days with some non-missing data during the run-in period are required.

Physical examination results will be only listed.

10.4.4 Prior, Maintained and Concomitant Medications

Previous medications will be summarized by treatment and overall, while maintained and concomitant medications will be summarized by treatment (for the assignment of medications to a category, see section 7.2.5).

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

Post-treatment medications 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 Safety and ITT populations. Percentages will be based on the number of subjects in the population.

10.5 Study drug / Investigational Medicinal Product

10.5.1 Background medication

Daily dose of previous ICS treatment for Asthma will be summarized by summary statistics and absolute counts (n) of subjects according to the dose category (Low Daily Dose and Medium Daily Dose), and the number of morning and evening puffs that the subject was instructed to take, both for QVAR 40 µg and QVAR 80 µg for ITT population. The clinically

comparable dose assigned will also be described categorically (Low Daily Dose, Medium Daily Dose).

Exposure and compliance will be summarized by summary statistics and absolute counts (n) and percentages (%) by the treatment that the subject will be randomized to and overall during the Run-in Period for the ITT populations. In addition, the number and percentage of subjects with the following compliance categories: satisfactory (65% - 135%) and unsatisfactory (<65%; >135%) levels of compliance and 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%], >140%) to the background medication will be summarized by treatment and overall during the Run-in Period.

10.5.2 Study drug

Treatment exposure and compliance during the Treatment Period will be summarized by summary statistics and absolute counts (n) by treatment using the ITT and Safety populations. 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. 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%], >140%).

10.5.3 Compliance with the use of Diary

Compliance with the use of Diary in Run-in Period and Treatment period 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.

10.6 Efficacy Results

10.6.1 Primary efficacy variable

The primary endpoint is the change from baseline in pre-dose morning FEV_1 at Week 8. The change from baseline in FEV_1 will be analyzed using a linear mixed model for repeated measurements 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 718 pMDI and placebo at Week 8 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 718 pMDI versus placebo will be demonstrated by a statistically significant difference (adjusted p-value < 0.05) favoring CHF 718 pMDI. 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 mean absolute FEV_1 values will be plotted over time for each of the treatment groups. These figures will be based on data from subjects in both ITT and PP populations (separate graphs for ITT and PP).

The mean change from baseline and adjusted mean change from baseline FEV_1 values will be plotted over time for each of the treatment groups. 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 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; in addition 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:

- *Change from baseline in pre-dose morning FEV_1 at Week 4*

The change from baseline in pre-dose morning FEV_1 at Week 4 will be analyzed using a linear mixed model for repeated measurements 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 change from baseline and adjusted mean change from baseline FEV_1 values will be plotted over time for each of the treatment groups.

- *Change from baseline in pre-dose morning FVC at Week 4 and Week 8*

The change from baseline in pre-dose morning FVC at Week 4 and Week 8 will be analyzed using a linear mixed model for repeated measurements 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 adjusted mean change from baseline FVC values will be plotted over time for each of the treatment groups.

- *Change from baseline in ACQ-7 score at Week 4 and Week 8*

The change from baseline in ACQ-7 score at Week 4 and Week 8 will be analyzed using a linear mixed model for repeated measurements 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 adjusted mean change from baseline in ACQ-7 score will be plotted over time for each of the treatment groups.

- *Change from baseline in average use of rescue medication (number of puffs/day) during inter-visit periods and entire treatment period*

The change from baseline to each inter-visit period and to the entire treatment period in the average use of rescue medication will be analyzed using a linear mixed model for repeated measurements as outlined in Section 8.2. See Section 7.1 for the definition of the inter-visit periods. 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 adjusted mean change from baseline in use of rescue medication will be plotted over time for each of the treatment groups.

- *Change from baseline in percentage of rescue medication-free days during inter-visit periods and entire treatment period*

The change from baseline to each inter-visit period and to the entire treatment period in the percentage of rescue medication-free days will be analyzed using a linear mixed model for repeated measurements as outlined in Section 8.2. See Section 7.1 for the definition of the inter-visit periods. 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 adjusted mean change from baseline in percentage of rescue medication free days will be plotted over time for each of the treatment groups.

- *Change from baseline in daily asthma symptoms scores during inter-visit periods and entire treatment period*

The change from baseline to each inter-visit period and to the entire treatment period in daily asthma symptoms score will be analyzed separately for morning and evening and also as a total (considering both morning and evening) using a linear mixed model for repeated measurements as outlined in Section 8.2. See Section 7.1 for the definition of inter-visit periods. 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 adjusted mean change from baseline in daily asthma symptoms scores will be plotted over time for each of the treatment groups.

- *Change from baseline in percentage of asthma symptoms-free days during inter-visit periods and entire treatment period*

The change from baseline to each inter-visit period and to the entire treatment period in percentage of asthma symptoms-free days will be analyzed using a linear mixed model for repeated measurements as outlined in Section 8.2. See Section 7.1 for the definition of inter-visit periods. 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 adjusted mean change from baseline in percentage of asthma symptoms-free days will be plotted over time for each of the treatment groups.

- *Change from baseline in percentage of asthma control days during inter-visit periods and entire treatment period*

The change from baseline to each inter-visit period and to the entire treatment period in percentage of asthma control days will be analyzed using a linear mixed model for repeated measurements as outlined in Section 8.2. See Section 7.1 for the definition of inter-visit periods. 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 adjusted mean change from baseline in percentage of asthma control days will be plotted over time for each of the treatment groups.

- *Change from baseline in morning and evening pre-dose PEF during inter-visit periods and entire treatment period*

The change from baseline to each inter-visit period and to the entire treatment period in morning and evening pre-dose PEF will be analyzed using a linear mixed model for repeated measurements as outlined in Section 8.2. See Section 7.1 for the definition of inter-visit periods. 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.

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 a TEAE. Only TEAEs will be included in the tables. 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, serious TEAEs, ADRs, 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.

Subjects who have multiple events in the same system organ class (SOC) and preferred term (PT) will be counted only once in the subject counts.

10.7.2 Vital Signs

Vital signs (systolic and diastolic blood pressure) and their changes from baseline (pre-dose on Day 1) on Week 4 and Week 8 will be summarized by treatment using descriptive statistics and the 95% CI of the mean.

10.7.3 ECGs

10.7.3.1 12-Lead ECGs

ECG parameters (HR, QTcF, QRS, and PR) will be summarized on Day 1 and Week 8 by treatment using descriptive statistics and the 95% CI of the mean. The nominal recorded value will be used in the calculation. In addition, their changes from baseline will be summarized using descriptive statistics and 90% CI.

In addition, the number and percentage of subjects with prolonged QTcF will be summarized using counts and percentages on Day 1, and Week 8 using the following thresholds:

- 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
- Change from baseline in QTcF >60 ms

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

- patients with a pacemaker already in place at study entry, identified by the presence of at least one of the following Preferred Terms in the medical/surgical history or concomitant diseases: “Cardiac pacemaker battery replacement”, “Cardiac pacemaker evaluation”, “Cardiac pacemaker insertion”, “Cardiac pacemaker replacement”, “Electrocardiogram pacemaker spike”, “Pacemaker generated arrhythmia”, “Pacemaker generated rhythm”, “Pacemaker syndrome”, “Cardiac assistance device user”;
- patients with a pacemaker implanted during the study, identified by a procedure coded with the Preferred Term “Cardiac pacemaker insertion” (other relevant cases may be identified in the Data Review Report). In this case, only the parameters assessed in a date ≥ 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”;
- 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

Shift tables will be presented for hematology and biochemistry parameters by treatment group at Day 1 and Week 8.

The categories for the shift tables are as follows:

- Low clinically significant
- Low not clinically significant
- Normal
- High clinically significant
- High not clinically significant

In addition, all laboratory data will be listed, with abnormal values flagged. Mean change from baseline (Visit 2) to the end of treatment in 24-h urinary free cortisol and creatinine will be calculated with its 95% CI by treatment group.

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, will be evaluated case by case during the Data Review Meeting.
The following rules on data re-allocation will be considered:

- Data collected at multiple visits (spirometry, ACQ score, vital signs, laboratory data, and ECG) recorded at the study termination visit for discontinued patients will be re-allocated by selecting the next visit at which the assessment was planned. For each assessment, only the visits at which the assessment was scheduled will be considered for re-allocation. This means that ECG and laboratory data can be re-allocated only to Visit 4. For example, if the last visit performed before the study termination visit was Visit 2, the data recorded at the study termination visit will be re-allocated to Visit 3 for spirometry, ACQ score, and vital signs, and to Visit 4 for 12-lead ECG and laboratory data. 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.
- For discontinued patients, efficacy data recorded in the diaries from the last visit performed before the study termination visit or the date of discontinuation onwards will be reallocated to the next expected inter-visit period;
- in case of missing intermediate visit not due to the re-allocation of data collected at the study termination visit (e.g., Visit 3 missing, but Visits 2 and 4 performed), an expected date for the missing Visit 3 will be imputed in order to define the inter-visit periods for diary data. The expected date for the missing Visit 3 will be imputed as follows: Visit 3 expected date = Visit 2 date + 28 days.
- Additional unscheduled/optional assessments 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.
- 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.

11 Table of Contents for the Tables, Listings and Figures

Key Frist Results (KFR) are identified with an "*".

Post-Text Tables

*Table 14.2.1.5: Analysis of Change from Baseline in Pre-dose Morning FEV1 at Week 8 – Sensitivity analysis (ICS dose as randomized) (ITT Population)
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