NCT05292586

STATISTICAL ANALYSIS PLAN

STUDY CODE No.: CLI-05993AB8-02

A 12 week, randomized, double-blind, multicenter, active controlled, 2-arm parallel group study testing the superiority of CHF 1535 pMDI 800/24µg total daily dose (fixed combination of extrafine beclomethasone dipropionate plus formoterol fumarate) compared to CHF 718 pMDI 800µg total daily dose (extrafine beclomethasone dipropionate) in adults with asthma on medium or high-dose inhaled corticosteroid

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Contents

List of Abbreviations

ACQ	Asthma Control Questionnaire
ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
AQLQ	Asthma Quality of Life Questionnaire
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Curve
BDP	Beclomethasone dipropionate
BID	Twice a Day
BLQ	Below Limit of Quantification
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CR	Copy Reference
CRP	C-Reactive Protein
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of Variation
DRM	Data Review Meeting
DRR	Data Review Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
ET	Early Treatment
ETD	Early Treatment Discontinuation
ETDV	Early Treatment Discontinuation Visit
EoS	End of Study Period
FDC	Fixed Dose Combination
FEV_1	Forced Expiratory Volume in the 1st second
FF	Formoterol Fumarate
FU	Follow-up
FVC	Forced Vital Capacity
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled CorticoSteroid
IRT	Interactive Response Technology

ITT	Intention-To-Treat
IWRS	Interactive Web Response System
LABA	Long Acting β_2 Agonist
LL	Lower Limit
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random
OR	Odds Ratio
PEF	Peak Expiratory Flow
PR	Time Interval Between the P and R wave in the ECG
PT	Preferred Term
QRS	Time Interval Between the Q and R and S wave in the ECG
QTc	Time interval between the Q and T waves in the ECG (corrected for HR)
QTcF	QT interval corrected using Fridericia's formulas
SABA	Short-Acting β2 Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TDD	Total Daily Dose
TEAE	Treatment Emergent Adverse Event
UL	Upper Limit
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

Version History

Version	Date	Change History
1.0	26 Aug 2024	*Final version 1.0*
2.0	27 Sep 2024	*Final version 2.0* • *Section 7.8.1. Baseline definition for ACQ-5 and ACQ-7 score was updated to clarify how to handle multiple assessments at week 0.* • *Section 8.6. Compliance calculation was updated to use the number of inhalations recorded in the questionnaire regardless the setting of electronic eDiary.* • *Section 8.6.2.3. the sentence 'if date of early discontinuation from the study equal to the date of Visit 2, then 2' was removed since it was in conflict with a previous statement 'If date of start of randomized treatment period = date of end of efficacy assessment period or early discontinuation from the study (i.e. no data collecting in the e-diary), compliance will be considered as missing'* • *For consistency across the SAP, the term 'End of randomized treatment period' was replaced by 'End of efficacy assessment period/ discontinuation'. Additionally, no definition of 'End of randomized treatment period' is described in SAP.* • *Section 9.2.1.1.1. the sentence 'see section number 9.2.1.1.1' was replaced 'see section number 9.1.1.1' since it was a typo.* • *Section 10.2.2. The 'local steroid effects' was added to the table class related adverse events as ICS class related event following a post-DRM decision.* • *Section 14.8. The division by thousand ('/1000') was removed to produce the results in the appropriate units.* • *Section 16. To be consistent with section 10.2.2 that state that 'The comparative analysis (i.e., estimation of risk difference and its 95% CI) will not be carried out if the total number of subjects with the event in the overall Safety Set is < 5.', a footnote with statement was added to Table 14.3.2.10, Table 14.3.2.11, Table 14.3.2.21, Table 14.3.2.22, Figure 14.3.1, Figure 14.3.2, Figure 14.3.3, Figure 14.3.4, Figure 14.3.5, Figure 14.3.6 and the sentence 'at least 10' was replaced by 'at least 5' in the notes for the above tables.*

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for Chiesi Farmaceutici S.p.A. protocol CLI-05993AB8-02: "*A 12 week, randomized, double-blind, multicenter, active controlled, 2-arm parallel group study testing the superiority of CHF 1535 pMDI 800/24µg total daily dose (fixed combination of extrafine beclomethasone dipropionate plus formoterol fumarate) compared to CHF 718 pMDI 800µg total daily dose (extrafine beclomethasone dipropionate) in adults with asthma on medium or high-dose inhaled corticosteroid (**FORCE2**)*".

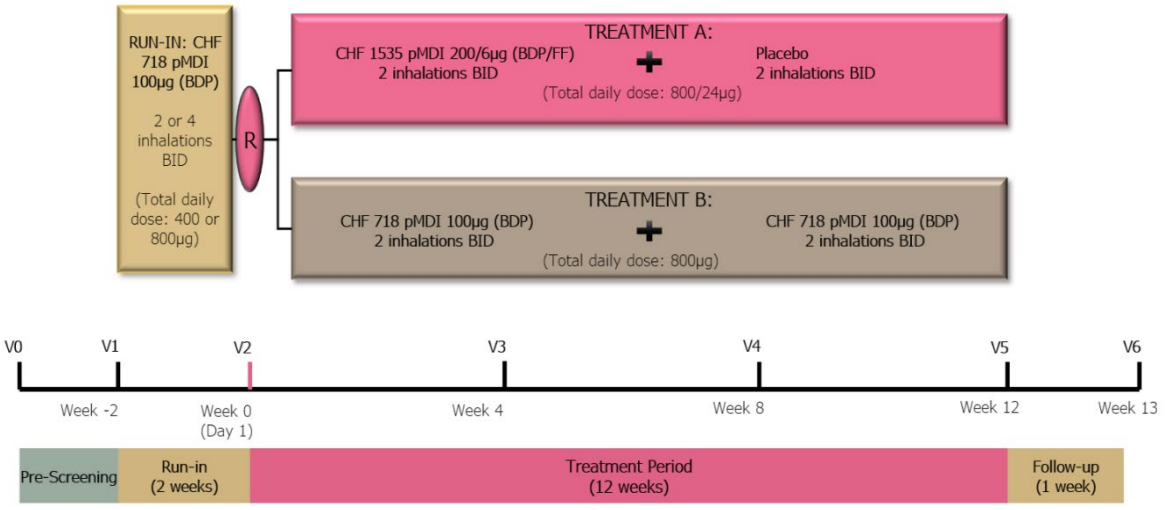
This analysis plan is based on the final protocol (version 2.0), dated 01 June 2023 and the final electronic case report form (eCRF) (version 7.0) dated 03 July 2023.
The SAP provides the description of the final analysis. In case of any deviations from this SAP, explanations will be provided in the Clinical Study Report (CSR).

ICON is contracted to support statistical analyses and is responsible for the production and quality control of all outputs described in this document.

2 Study Design

This is a phase III, randomized, double-blind, active controlled, 2-arm parallel group study to demonstrate the superiority of CHF 1535 pMDI 800/24µg total daily dose (TDD) compared to CHF 718 pMDI 800µg in terms of change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12 in adult subjects with asthma on medium or high dose inhaled corticosteroids (ICS) or on medium dose ICS plus long-acting β2-agonist (ICS/LABA).

The study entails three periods: a run-in period of 2-weeks duration, a treatment period of 12 weeks duration, and a post-treatment follow-up period of 1 week.



A total of 6 clinic visits (V0 to V5) and a follow-up call will be performed for any subject completing the trial, as follows:

- A pre-screening visit (V0) will be carried out to fully explain the study to potential subjects, to obtain the written informed consent from the subject and to instruct the subject on screening visit procedures (such as medication restrictions).
- A screening visit (V1, Week -2) will help establishing the eligibility of subjects for inclusion in the study (including routine hematology and blood chemistry, medical history, physical examination, vital signs, a 12-lead Electrocardiogram (ECG), Asthma Control Questionnaire 7 (ACQ-7) (prior to spirometry), spirometry including FEV_1 reversibility after albuterol intake, and training for the use of inhalers and diary/peak flow meter).
- A 2-week open-label run-in period will be carried out after V1, where screened subjects who were on a medium dose ICS or medium dose ICS/LABA prior to the study will be put on CHF 718 pMDI 100µg 2 inhalations BID (TDD 400µg) during the 2-week run in period; and screened subjects who were on a high dose ICS prior to the study will be put on CHF 718 pMDI 100µg 4 inhalations BID (TDD 800µg) during the 2-week run in period.
- After the run-in period, eligible subjects will be randomized to one of the 2 study treatment arms (using a 1:1 allocation ratio) for 12 weeks (V2, Week 0/Day 1):
  - **Test Treatment – CHF 1535 pMDI 800/24µg TDD and Placebo**: Fixed combination of extrafine Beclomethasone dipropionate (BDP) 200µg plus FF 6µg (BDP/FF) puffs from each inhaler BID. BDP/FF 200/6µg per actuation, 2 inhalations (puffs) BID, total daily dose (TDD) 800/24µg;
  - **Reference Treatment – CHF 718 pMDI 800µg TDD**: BDP 100µg. BDP 100µg per actuation, 4 inhalations (puffs) BID, total daily dose (TDD) 800µg.
- After the randomization visit (V2, Week 0), subjects will be assessed after 4 (V3, Week 4), 8 (V4, Week 5) and 12 weeks of treatment (V5, Week 12) at the clinic. At V2 (Week 0) and V5 (Week 12), ACQ-7 will be performed prior to spirometry. Spirometry will be performed at -45 min and -15 min pre-dose and at 5 min, 15 min, 30 min, 1hr, 2hr, 3hr, 6hr, 9hr, 11.5hr and 12hr post-dose. Vital signs and 12-lead ECG will be performed pre-dose and at 30 mins, 1h, 4h, and 12h post-dose. At V3 (Week 4) and V4 (Week 8), pre-dose spirometry (i.e., no serial spirometry will be performed), pre-dose vital signs and 12 lead ECG, as well as ACQ-7 will be performed.
- A safety follow-up phone call will be done by the investigator 1 week after V5 or Early Treatment Discontinuation visit (V6 or ETD, Week 13) to check the status of unresolved adverse events (AEs) and to record any new AEs that have occurred after the last visit as well as the related concomitant medications.
- AEs and serious adverse events (SAEs) will be monitored throughout the study.

The study duration from V0 to V6 will be about 16 weeks. The subjects who discontinue study treatment should not be considered automatically withdrawn from the study (except if the reason is consent withdrawal or lost to follow up). These subjects will be encouraged to remain in the study and complete all remaining protocol-specified visits (while off investigational treatment) to assess lung function, adverse events, SAEs, and concomitant medications post investigational treatment.

The start of the trial is defined as the date of first site initiation visit in the trial.
The end of the trial is defined as the last contact of the last subject in the trial:

- Last follow-up contact;
- Last study visit, if the last subject in the trial is discontinued from the treatment and agrees to remain in the study.

2.1 Study Schedule

	Pre-screening	Run-in	Treatment Period				Follow Up Call	Early** Term
Visits	V0	V1 Screening	V2 Rand.*	V3	V4	V5	V6	
Time (weeks)	-3	-2	0	4	8	12	13	
Visit Windows (days)			± 2	± 2	± 2	±2	± 2	
Informed Consent Form	✓							
Demographic Data	✓							
IRT Visit Confirmation Call	✓	✓	✓	✓	✓	✓	✓	✓
Inclusion/ Exclusion Criteria		✓						
Eligibility Recheck[1]			✓					
Medical History/ Previous Meds & Smoking History		✓						
Concomitant Medications		✓	✓	✓	✓	✓	✓	✓
Adverse Events Assessment		✓	✓	✓	✓	✓	✓	✓
Full Physical examination		✓				✓		✓
Oropharyngeal examination		✓	✓	✓	✓	✓		✓
Hematology and Blood Chemistry		✓				✓		✓
Serum pregnancy test (WOCBP)		✓				✓		✓
Urine pregnancy test (WOCBP)		✓	✓	✓	✓	✓		✓[6]
Spirometry pre/post albuterol[2], Vital signs & ECG pre-albuterol		✓						
Spirometry V2 & V5: serial[4,5] V3 & V4: pre-dose only			✓	✓	✓	✓		✓[7]
Vital signs V2 & V5: serial[3] V3 & V4: pre-dose vital signs only			✓	✓	✓	✓		✓[7]
ECG: V2 & V5: serial ECG[3] V3 & V4: pre-dose ECG only			✓	✓	✓	✓		✓[7]
ACQ-7 Questionnaire			✓	✓	✓	✓		✓
Training (pMDI, eDiary, Peak Flow Meter)		✓	✓					
eDiary/Peak Flow Meter completion		(daily)	(daily)	(daily)	(daily)			
Dispensation (D)/ return (R) of rescue albuterol		D	D/R	D/R	R			
Dispensation (D)/ return (R) of run-in medication		D	R					
Study Drug dispensation (D)/ return & Accountability (R)			D	D/R	D/R	R		R
Subject eDiary/Peak Flow Meter dispensation (D)/ Return (R)		D	D/R	D/R	D/R	R		R
Morning dose of Study Drug Administration			✓	✓	✓	✓		✓
Review of eDiary/Peak Flow Meter and study drug compliance			✓	✓	✓	✓		✓

*Rand.: Randomization
**Early Term: Early Termination for randomized subjects withdrawn from study treatment before week 12

1- Eligibility re-check only for inclusion criteria 5, 7, 8. 9 and exclusion criteria 2, 3, 13, 16, 26.
2- Spirometry will be carried out at baseline and repeated within 30 minutes after the inhalation of 4 puffs of albuterol.
3- Vital signs and 12-Lead ECG- pre-dose and 30 min, 1h, 4 h and 12 h post-dose
4- Pre-dose FEV_1: -45min and -15min before administration of study drug at (V2 and V5/ET).
5- Post-dose serial spirometry (FEV_1): 5min, 15min, 30min, 1h, 2h, 3h, 6h, 9h, 11.5h, 12h (V2 and V5/ET)

6- Urine pregnancy test to be done only if serum is not collected.
7- Early Termination visit – Pre-dose vital signs, ECG and spirometry.

2.2 Treatment Allocation

A balanced block randomization scheme stratified by prior asthma therapy at screening/study entry (3 levels – "medium dose ICS/LABA" vs. "medium dose ICS" vs. "high dose ICS") and US region (4 levels – "Northeast" vs. "Midwest" vs. "South" vs. "West"; see APPENDIX I for full details) will be prepared via a computerized system. Subjects will be centrally assigned to one of the two treatment arms with a 1:1 ratio.
An Interactive Response Technology (IRT) system will be used at each visit (from pre-screening to follow-up call) to record subject status.
Subject number will be centrally assigned, through the IRT, during the pre-screening visit (Visit 0).
Subject numbers will consist of a 9 digit-number:

- the 6 first digits correspond to the center number (first 3 digits for the country number corresponding to the ISO country codes and 3 last progressives for the site);
- the 3 last digits to the screening number (allocated in a chronological way in each site).

The Investigator, or designee, at the sites will call the IRT system to screen, randomize subjects and assign treatment kits according to the sequence described in the randomization list. The IRT will track also subject screen failures and discontinuations from the treatment and from the study.

3 Study Objectives

3.1 Primary Objective(s)

- To demonstrate the superiority of CHF 1535 pMDI 800/24µg TDD compared to CHF 718pMDI 800µg TDD in terms of change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Week 12.

3.2 Secondary Objectives

3.2.1 Key Secondary Objective(s)

- To demonstrate the superiority of CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in peak FEV_1 within the first 3 hours post dose at Week 12.

3.2.2 Other Secondary Objectives

- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Week 0.
- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in peak FEV_1 within the first 3 hours post-dose at Week 0.
- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in trough FEV_1 at Week 12.

- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in pre-dose morning FEV_1 at Week 4, 8 and 12.
- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in average morning PEF over 12-week treatment period.
- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in average evening PEF over 12-week treatment period.
- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of FEV_1 responders (i.e., change ≥100 mL) for pre-dose morning FEV_1 at Week 4, 8 and 12.
- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of FEV_1 responders (i.e., change ≥100 mL) for trough FEV_1 at Week 12.
- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in terms of ACQ-7 and ACQ-5 at Week 12.
- To evaluate CHF 1535 pMDI 800/24µg TDD compared to CHF 718 pMDI 800µg TDD in terms of change from baseline in percentage of rescue medication free days and asthma symptom free days over 12-week treatment period.
- To assess the safety and the tolerability of the study drugs.

4 Study Variables

4.1 Efficacy Variables

4.1.1 Primary Efficacy Variable(s)

- Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Week 12.

4.1.2 Secondary Efficacy Variables

4.1.2.1 Key Secondary Efficacy Variable(s)

- Change from baseline in peak FEV_1 within the first 3 hours post dosing at Week 12.

4.1.2.2 Other Secondary Efficacy Variables

- Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Week 0.
- Change from baseline in peak FEV_1 within the first 3 hours post dosing at Week 0.
- Change from baseline in trough FEV_1 at Week 12.
- Change from baseline in pre-dose morning FEV_1 at Week 4, 8 and 12.
- Change from baseline in average morning PEF measured by subjects at home over the 12-week treatment period.
- Change from baseline in average evening PEF measured by subjects at home over the 12-week treatment period.
- Proportion of subjects classified as responder (change from baseline ≥100 mL) in pre-dose morning FEV_1 at Week 4, 8 and 12.

- Proportion of subjects classified as responder (change from baseline ≥100 mL) in trough FEV_1 at Week 12.
- Change from baseline in ACQ-7 and ACQ-5 score at Week 12.
- Change from baseline in percentage of rescue medication free days over 12-week treatment period.
- Change from baseline in percentage of asthma symptom free days over 12-week treatment period.

4.2 Safety Variables

- Treatment Emergent Adverse Events (TEAE), Adverse Drug Reactions (ADRs), Serious TEAEs, serious ADRs, TEAEs leading to study withdrawal, and TEAEs leading to death.
- Vital signs (systolic and diastolic blood pressure).
- 12-lead ECG parameters: heart rate (HR), QTcF, PR and QRS.
- Standard hematology and blood chemistry.

5 Sample Size

The sample size has been calculated to demonstrate the superiority of CHF 1535 pMDI 800/24µg TDD over CHF 718 pMDI 800µg TDD in terms of the primary and key secondary endpoint.

A discontinuation rate from the randomized study treatment of approximately 10% at Week 12 has been considered.

A total of 580 subjects will be randomized according to a 1:1 ratio to either CHF 1535 pMDI 800/24µg TDD or CHF 718 pMDI 800µg TDD (i.e., 290 subjects per group). This sample size will provide, using the main estimand:

- Approximately 89% power to detect a mean difference between groups of 108 mL in favor of CHF 1535 pMDI 800/24µg TDD on change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12 at a two-sided significance level of 0.05, assuming a SD of 409 mL The assumed mean difference of 108 mL represents a weighted average between two means: a mean difference between groups of 120 mL while on treatment (assuming 90% of the randomized subjects) and a mean difference between groups of 0 mL while off-treatment (assuming 10% of the randomized subjects).
- Approximately 90% power to detect a mean difference between groups of 117 mL in favor of CHF 1535 pMDI 800/24µg TDD on change from baseline in peak FEV_1 within the first 3 hours post dose at Week 12 at a two-sided significance level of 0.05, assuming a SD of 434 mL. The assumed mean difference of 117 mL represents a weighted average between two means: a mean difference between groups of 130 mL while on treatment (assuming 90% of the randomized subjects) and a mean difference between groups of 0 mL while off treatment (assuming 10% of the randomized subjects).

Thus, considering the main estimand analysis, an overall study power of at least 80% for the primary and the key-secondary efficacy endpoint will be ensured."

6 Analysis Sets

The definitions of the analysis sets are summarized below.

Patients enrolled in sites, which are/will be identified major Good Clinical Practice violators, will be excluded from all analyses and all analysis sets. This includes (but is not limited to) sites who have been identified of misconduct.

In confirmed cases of patients randomized more than once, only the data associated with the first randomized treatment period for which at least one dose of study treatment was received will be used in any analysis set. The safety data (i.e., adverse events at a minimum) associated with any other randomized period will be documented separately in the DRR and CSR as applicable.

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

6.1 Safety Set

Safety set includes all randomized subjects who receive at least one dose of study treatment.

The Safety set will be used in the analysis of all safety variables. In case of deviation between as-randomized treatment and treatment actually received, the treatment actually received will be used in the analyses (i.e., an as-treated analysis will be performed).

6.2 Intention-To-Treat Set (ITT)

Intention-to-Treat (ITT) set includes all randomized subjects who receive at least one dose of the study treatment.

The ITT set will be used in the analysis of all efficacy variables. In case of deviation between as-randomized treatment and treatment actually received, the subject will be reported under the randomized treatment group for all analyses performed on the ITT set (i.e., an as-randomized analysis will be performed).

6.3 Other Sets Defined for Tables and Listings

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

- Enrolled set includes all subjects who provided informed consent for the study.
- Randomized set includes all subjects randomized to study medication.

7 General Considerations for Statistical Analysis

7.1 Statistical Significance

Unless otherwise stated, all tests of hypotheses will be two-sided and conducted at the 0.05 significance level, and all confidence intervals will be two-sided at the 95% confidence level.

7.2 Multiplicity

The primary and key-secondary efficacy endpoints will be tested for statistical significance following a hierarchical strategy to control the familywise type I error rate using the main estimand. Each test will be considered confirmatory only if the tests at all the previous steps are successful. The hierarchy for the primary and key secondary endpoints is as follows:

Step 1 – If the p-value resulting from the comparison between test and reference treatment on primary endpoint (i.e., change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12), at a 2-sided 5% significance level, is

- greater than or equal to alpha=0.05, the procedure is stopped, and no results should be considered as statistically significant.
- smaller than alpha=0.05, the comparison is declared as statistically significant, and the procedure should move to step 2.

Step 2 – If the p-value resulting from the comparison between test and reference treatment on key-secondary endpoint (i.e., change from baseline in peak FEV_1 within the first 3 hours post dose at Week 12), at a 2-sided 5% significance level, is

- greater than or equal to alpha=0.05, the procedure is stopped, and only primary endpoint is declared as statistically significant.
- smaller than alpha=0.05, both primary and key secondary endpoint are declared as statistically significant.

All sensitivity analysis and all other secondary efficacy analyses will be regarded as supportive or exploratory and as such no formal adjustment for multiplicity will be made.

7.3 Handling of Missing Data

7.3.1 Missing Data Analysis Methods

The number of subjects with missing data will be presented under a "Missing" category. Unless otherwise stated, missing values will not be included in the denominator count when calculating percentages.

When quantitative variables are being summarized, only the non-missing values will be evaluated for calculating summary statistics.

7.3.1.1 Derived Measures

Several derived variables will be used in this study to measure efficacy endpoints: FEV_1 $AUC_{0\text{-}12h}$, Pre-dose FEV_1, Trough FEV_1, Peak FEV_1, variables based on daily data measurements, and ACQ-5 and ACQ-7 scores. As such, missing data in this type of variables can occur on the partial measures. Unless otherwise stated, missing data will be handled as described below.

Pre-dose FEV_1: Pre-dose FEV_1 is defined as the arithmetic mean of 45 minutes and 15 minutes pre-dose FEV_1 measurements. Missing values will be handled as follows:

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

FEV_1 $AUC_{0\text{-}12h}$: FEV_1 measurements are collect at timepoints: -45 min and -15 min pre-dose and 5 min, 15 min, 30 min, 1h, 2h, 3h, 6h, 9h, 11.5h and 12 h post-dose. In the calculation of FEV_1 $AUC_{0\text{-}12h}$ normalized by time, FEV_1 missing values will be handled as follows:

- If the pre-dose FEV_1 value is not available (see definition above), the entire curve will be considered as missing.
- If the 12h FEV_1 value is not available, the value of the previous timepoint will be carried over; the time associated with this timepoint will be the time of the last study medication intake plus 12 hours.
- If a single (isolated) missing FEV_1 value (not pre-dose nor last value) is not available, missing value will be replaced by linear interpolation using the two adjacent values. Imputation is performed as follows, assuming that the value at timepoint t is missing, and both the last actual assessment taken prior to timepoint t, which is timepoint (t-1), and the first actual assessment taken after timepoint t, which is timepoint (t+1), are available.

$$value_t = value_{t-1} + \left[\frac{(value_{t+1} - value_{t-1}) * (time_t - time_{t-1})}{time_{t+1} - time_{t-1}}\right]$$

- If 2 or more consecutive post-dose time points have missing FEV_1 values, the FEV_1 $AUC_{0\text{-}12h}$ will be considered as missing.
- If in total 3 or more of the post-dose time points have missing FEV_1 values, the FEV_1 $AUC_{0\text{-}12h}$ will be considered as missing.

Trough FEV_1: Trough FEV_1 is defined as the arithmetic mean of 11.5h and 12h post-dose FEV_1 measurements. Missing values will be handled as follows:

- If one of the FEV_1 measurements at 11.5h and 12h post-dose is not available, then the non-missing measurement will be taken as the trough FEV_1 value.
- If no measurement is available, then the trough FEV_1 value will be considered as missing.

Peak FEV_1: Peak FEV_1 is defined as the maximum value among 5 min, 15 min, 30 min, 1h, 2h and 3h post-dose FEV_1 measurements. Missing values will be handled as follows:

- If 2 or more FEV_1 measurements at 5 min, 15 min, 30 min, 1h, 2h and 3h post-dose are not available, then the peak FEV_1 value will be considered as missing.

Daily data measurements: Morning and evening PEF, use of rescue medication, daily asthma symptoms, percentage of rescue medication free days and asthma symptom free days are derived from daily eDiary data collected. Missing values will be handled as follows:

- If a minimum of 7 days is not available in the run-in period and in each inter-visit period (i.e., [Week 0 – Week 4]; [Week 4 – Week 8] and [Week 8 – Week 12]), then the variable derived from this daily data will be consider as missing for the run-in period or for the inter-visit period in which the missing data condition occurred.
- In case of missing day (i.e., please refer to Section 7.8.1, 9.2.2.5, 9.2.2.6, 9.2.2.10, and 9.2.2.11 for the definition of complete/missing day for each parameter collected in eDiary), the day will be excluded from the average for continuous variables and will not be included in the denominator count when calculating percentages for categorical variables.

ACQ-7 and ACQ-5 questionnaire: Missing values will be handled as follows:

- If at least one missing data occurs in one of the seven items of ACQ-7 or in one of the five items of ACQ-5, then total score will be set as missing for ACQ-7 or for ACQ-5, respectively.

7.3.1.2 Continuous Efficacy Endpoints

Analysis of Covariance (ANCOVA) will use all available data (i.e., both data collected on-treatment and data collected off-treatment) and imputed missing data of subjects prematurely discontinuing from the study, in order to estimate the mean treatment effect.

Unless otherwise stated, for all continuous efficacy endpoints, missing data will be imputed according to the following stages:

- Stage #1: Intermittent missing data (i.e., a missing value followed by an observed on-treatment or off-treatment value), due to *Missed visit or assessment not performed/not evaluable at intermediate visit*, will be imputed using multiple imputation (MI), in order to achieve a monotone missing data pattern;
- Stage #2: Monotone missing data, commonly due to *Early discontinuation from study*, will be imputed using multiple imputation, in order to achieve a complete data scenario.

Intermittent missing data (on-treatment and off-treatment) will be imputed under the Missing At Random (MAR) assumption based on a joint multivariate normal imputation model (using PROC MI with Markov Chain Monte Carlo [MCMC] procedure). More detail can be found below in section 7.3.1.2.1.

Monotone missing data will then be imputed as follow:

- *Imputation of monotone missing data using available off-treatment data:* In case of sufficient off-treatment data on all subjects (i.e., from both treatment arms), the imputation will be done using available off-treatment data for both treatment arms. This imputation technique will be applied if at least 5% of the analyzed population (ITT) consented to continue the study after treatment discontinuation and attended visit 5 off-treatment. This approach targets the off-treatment effect that would have been observed if all subjects discontinued from study drug had consented to continue the study. This approach assumes that subjects who discontinue the study tend to have similar values on the endpoint, compared to those who discontinues the drug but not the study. More details can be found below in section 7.3.1.2.2.
- *Copy reference approach (CR):* In case of no sufficient off-treatment data (as described above) on all subjects, such that the previous imputation cannot be performed, the imputation will be based on the MAR approach for the reference arm and for the on-treatment missing data of the test arm, and on the CR approach for the off-treatment missing data of the test arm. This latter approach assumes that subjects who discontinue the study tend to have similar values on the endpoint, compared to those who are in the reference arm (CHF 718 pMDI 800µg TDD arm), including both on-treatment and off-treatment data. More details can be found below in section 7.3.1.2.3.

As a sensitivity analysis, and only for the primary and key secondary endpoints, monotone missing data due to *Early discontinuation from study* will be imputed as follow:

- *Two-dimensional tipping point approach:* the imputation will assume that all unobserved subjects will have a worse or better response than the observed ones, by adding or subtracting a ‘delta’ parameter to the imputed values. Under this approach, a

variations in assumptions about missing outcomes in the two treatment arms will be explored to identify the assumptions leading to a change in the conclusions – i.e., under which adjustment ('delta') the result is no longer statistically significant. More detail can be found below in section 7.3.1.2.4.

7.3.1.2.1 Imputation of Intermittent Missing Data

Imputation of Intermittent Missing Data (On-Treatment and Off-Treatment) will be carried out (see the Sample SAS code in section 14.5) by means of a multiple imputation (MI) procedure based on MAR assumption using the joint modelling approach in order to obtain monotone missing data patterns (using PROC MI with MCMC procedure and with the option IMPUTE=MONOTONE). Only missing values which causes non-monotone missing pattern will be imputed in this preliminary step. As an example, the imputation will be performed considering the following variables in the following order:

1. Treatment
2. Region
3. Prior asthma therapy
4. Baseline value of continuous efficacy endpoint
5. Post-baseline continuous efficacy endpoint values (e.g., from Visit 2 (Week 0) to Visit 5 (Week 12)).

One thousand imputations will be performed.

7.3.1.2.2 Imputation of Monotone Missing Data Using Available Off-treatment Data

It is a step-by-step procedure starting from the first planned post-baseline visit / inter-visit period (for eDiary based endpoints only) and considering separately each post-baseline study visit / inter-visit period (for eDiary based endpoints only). The approach and the steps described below refer to study visits, as this applies to primary, key secondary and majority of other secondary endpoints. To generalize for eDiary based secondary endpoints, the inter-visit periods should be considered instead. The approach used in this procedure is the one proposed by James Roger [12] and in general assumes that missing data at Visit N can be imputed conditioning on:

- On-/off-treatment status at Visit N.
  This indicator variable will be always populated, regardless of whether the assessment is collected or not.
- Residuals for each prior post-baseline visit (obtained by comparing the observed or imputed values with the predicted values from a linear model);
- The assumption that the correlation between residuals for any given prior post-baseline visit and Visit N do not differ by treatment group or on-/off-treatment status.

The following steps will be carried out (see the Sample SAS code section 14.6):

- **Step 1 - First Planned Post-Baseline Assessment (e.g., Visit 2)**
  1.1 Preliminary check
  A regression model will be carried out, on the first of the 1000 imputations of the monotone dataset, considering the value of the continuous efficacy endpoint at 1st post baseline assessment (e.g., Visit 2) as dependent variable and the following as independent variables:
  1. Treatment
  2. Region

3. Prior asthma therapy
4. Baseline value of continuous efficacy endpoint
5. Indicator variable identifying if the assessment at Visit 2 is on-treatment or off-treatment
6. Treatment by indicator (as above) interaction.

The aim of this preliminary step is to check if the estimation of the corresponding regression coefficients is successful and to check the "stability" of the model assessing the estimation of the standard error of the treatment difference vs. the estimation of the treatment difference.

In case one or more regression coefficients included in the MODEL statement are not estimated successfully (in case of categorical variables, the coefficients related to all the variable levels should be estimable) or if the estimation of the standard error of the treatment difference is greater than 10 times the size of the estimate of treatment difference, then the algorithm will stop and this imputation techniques will be disregarded. Missing data for the main estimand will then be imputed according to the Copy-Reference approach, as described in section 7.3.1.2.3.

1.2 Multiple imputation procedure for missing values at Visit 2

This step will be performed only in presence of missing data at Visit 2, otherwise the step will be skipped, and the algorithm will move to step 1.3.

A regression-based imputation of the value of the continuous efficacy endpoint at Visit 2 will be carried out, on all the 1000 imputations of the monotone dataset, using an imputation model identical to that used for the preliminary check.

1.3 Estimation of residuals for Visit 2

The same linear model used for the preliminary check will be estimated on all the 1000 imputations of the monotone dataset.

The purpose of this linear model is to estimate the predicted values for the continuous efficacy endpoint at Visit 2.

The residual values for Visit 2 will be obtained:

- (in case of step 1.2 performed) calculating the difference between observed or imputed values, obtained from Step 1.2, and these obtained predicted values;
- (in case of step 1.2 skipped) directly from the residual of the model specified above.

- **Step 2 - Subsequent Planned Post-Baseline Assessment (i.e., Visit X)**

2.1 Preliminary check

A regression model will be carried out, on the first of the 1000 imputations of the dataset including the residual from previous visits, considering the value of the continuous efficacy endpoint at Visit X as dependent variable and the following as independent variables:

1. Residual at all previous visits
2. Treatment
3. Region
4. Prior asthma therapy
5. Baseline value of continuous efficacy endpoint
6. Indicator variable identifying if the assessment at Visit X is on-treatment or off-treatment
7. Treatment by indicator (as above) interaction.

The same considerations as for the preliminary check in Step 1.1 (see above) apply.

2.2 Multiple imputation procedure for missing values at Visit X

This step will be performed only in presence of missing data at Visit X, otherwise the step will be skipped, and the algorithm will move to step 2.3.
A regression-based imputation of the value of the continuous efficacy endpoint at Visit X will be carried out, on all the 1000 imputations of the dataset including the residuals from previous visit, using an imputation model identical to that used for the preliminary check.
2.3 Estimation of residuals for Visit X
The same linear model used for the preliminary check will be estimated on all the 1000 imputations of dataset including the residuals from previous visit (the same one used as input dataset in Step 2.2, not including the imputed values for Visit X).
The purpose of this linear model is to estimate the predicted values for the continuous efficacy endpoint at Visit X.
The residual values for Visit X will be obtained:

- (in case of step 2.2 performed) calculating the difference between observed or imputed values, obtained from Step 2.2, and these obtained predicted values;
- (in case of step 2.2 skipped) directly from the residual of the model specified above.

Of note, this step will not be performed for the final visit, where only the preliminary check (Step N.1) and the multiple imputation procedure (Step N.2) will be performed.

- **Step N+1 – Analysis**: For each of the 1000 complete imputed datasets coming from Step N.2, the change from baseline in the continuous efficacy endpoint of interest will be analyzed separately at each visit / inter-visit period on the ITT set using an ANCOVA model including treatment group, region and prior asthma therapy as fixed effects, and baseline value (see section 7.8.1) as covariates.
- **Step N+2 – Combine the Results**: Results derived from Step N+1 will be combined using Rubin's rule.

7.3.1.2.3 Imputation of Monotone Missing Data Using Copy Reference (CR) Approach

For CR approach, the following steps will be carried out (see the Sample SAS code section 14.7).
The approach and the steps described below refer to study visits, as this applies to primary, key secondary and majority of other secondary endpoints. To generalize for eDiary based secondary endpoints, the inter-visit periods should be considered instead.

- **Step 1.1 – Imputation of Missing Data for Reference Treatment Group (i.e., both On-Treatment and Off-Treatment) and On-Treatment Missing Data for Test Treatment Group**: Imputation of both on-treatment and off-treatment missing data for reference treatment group (i.e., CHF 718 pMDI 800µg TDD arm) and on-treatment missing data for test treatment group (i.e., CHF 1535 pMDI 800/24µg TDD) will be carried out (see the Sample SAS code section 14.7) on all the 1000 imputations of the monotone dataset, by means of a multiple imputation (MI) procedure based on MAR assumption using a regression-based imputation. As an example, the imputation will be performed considering the following variables in the following order:
    1. Treatment
    2. Region
    3. Prior asthma therapy
    4. Baseline value of continuous efficacy endpoint

5. Post-baseline values of continuous efficacy endpoint (e.g., from Visit 2 (Week 0) to Visit 5 (Week 12)).

- **Step 1.2 – Imputation of Off-Treatment Missing Data for Test Treatment Group**: A regression-based imputation will be performed on all the 1000 imputed dataset created in Step 1.1. The imputation will be based on the data distribution of the CHF 718 pMDI 800µg TDD group (i.e., the reference treatment group, including both on-treatment and off-treatment data) for off-treatment missing data of the CHF 1535 pMDI 800/24µg TDD group only (i.e., the off-treatment missing data of the test treatment group). The imputation model will correspond to the one used in Step 1.1, except for the exclusion of the treatment effect. This analysis mimics the case where subjects who discontinue from the CHF 1535 pMDI 800/24µg TDD group are switched to the CHF 718 pMDI 800µg TDD group.
- **Step 2 – Analysis**: For each of the 1000 complete imputed datasets, the change from baseline in the continuous efficacy endpoint of interest will be analyzed separately at each visit / inter-visit period on the ITT set using an ANCOVA model including treatment group, region and prior asthma therapy as fixed effects, and baseline value (see section 7.8.1) as covariates.
- **Step 3 – Combine the Results**: Results derived from Step 2 will be combined using Rubin's rule.

7.3.1.2.4 Two-dimensional Tipping Point Approach

A two-dimensional tipping point analysis will explore the potential effect of missing data on the robustness of the results by using different assumptions regarding the primary and key-secondary endpoints in subjects who prematurely withdraw from the study.
This method evaluates several combinations of an arbitrary shift value (i.e., delta) added to the imputed missing values until the analysis reaches a "tipping point", at which a particular combination of imputed missing outcomes reverses the study conclusions (i.e., under which treatment effect is no longer statistically significant in favor of the test treatment), as summarized by the treatment comparison and its associated p-value [11] (i.e., p-value ≥ 0.05).
This sensitivity analysis foresees, under the MNAR assumption, multiple combinations of shift parameters, which adjust the imputed values for observations of both CHF 1535 pMDI 800/24µg TDD and CHF 718 pMDI 800µg TDD arms, stemming from the main estimand of the primary and key-secondary analysis (i.e., either the imputation using off-treatment data or the imputation using the copy-reference approach). This sensitivity analysis will only be conducted only if significant results in favor of the test treatment (i.e., p-value < 0.05) is found in the main analysis of the endpoint.
Subjects who prematurely withdraw from the study will have missing data imputed according to the approaches described in section 7.3.1.2.2 or section 7.3.1.2.3. Then, an arbitrary shift value (i.e., delta) will be added to the imputed values prior to the analysis of the imputed datasets and combination of the results. These deltas will vary independently for CHF 1535 pMDI 800/24µg TDD and CHF 718 pMDI 800µg TDD arms. In this analysis, increasing degrees of worsening or improvement after withdrawal will be evaluated both for CHF 1535 pMDI 800/24µg TDD and CHF 718 pMDI 800µg TDD arms. Therefore, delta will vary from -1 to 0 L with increments of 0.05 L for both the primary and the key-secondary endpoint. The increment and the range may be refined based on the analysis results and the location of the tipping point.

The general logic of such a strategy is as follows (see the sample SAS code section 14.8):

- **Step 1– "Delta" Selection**: Select "delta" values within the defined range for CHF 1535 pMDI 800/24µg TDD and CHF 718 pMDI 800µg TDD arms, respectively.
- **Step 2 – Addition of "delta" to Imputed Missing Values for Subjects Prematurely Withdrawing from Study**: Starting from the 1000 complete imputed datasets originating for the main estimand from either the imputation using the off-treatment data approach or the imputation using the copy-reference approach, the arbitrary shift value (i.e., delta) will be added only to the values which were imputed for those subjects who prematurely withdraw from the study (i.e., only the missing data imputed with either off-treatment data approach or copy-reference approach). One specific delta value will be applied to missing data for subjects of the CHF 1535 pMDI 800/24µg TDD arm and another specific delta value will be applied to missing data for subjects of the CHF 718 pMDI 800µg TDD arm.
- **Step 3 – Analysis**: For each of the 1000 complete imputed datasets with the addition of deltas, the continuous efficacy endpoint of interest will be analyzed on the ITT set using an ANCOVA model including treatment group, region and prior asthma therapy as fixed effects, and baseline value (see Section 7.8.1) as covariates.
- **Step 4 – Combine the Results**: Results derived from Step 3 will be combined using Rubin's rule.
- **Step 5 – Repetition of the Procedure for each "Delta"**: Repeat all the above steps from 1 to 4 choosing different delta value CHF 1535 pMDI 800/24µg TDD and CHF 718 pMDI 800µg TDD arms respectively, as many times as required to process all combinations of the pre-defined delta values for CHF 1535 pMDI 800/24µg TDD and CHF 718 pMDI 800µg TDD arms.
- **Step 6– Final Assessment**: Assess the estimates from Step 5 and identify the tipping-points for the delta shift parameters, such that the p-value obtained at Step 4 is greater than or equal 0.05. A shift table will display the treatment difference and p-value for each combination of delta values between CHF 1535 pMDI 800/24µg TDD and CHF 718 pMDI 800µg TDD arms. A graphical representation of the tipping point analysis could be also considered.

7.3.1.3 Dichotomous Efficacy Endpoints

For the dichotomous endpoints that are derived from continuous variables (e.g., proportion of subjects with a change from baseline ≥100 mL in pre-dose morning FEV_1), and are planned to target the same estimand as described for primary and key-secondary endpoints, imputation of missing data will be based on the completed datasets obtained as described for continuous variables in section 7.3.1.2 (only steps after dichotomizing the variable are different – more details can be found in sections 7.3.1.3.1 and 7.3.1.3.2).

7.3.1.3.1 Imputation of Monotone Missing Data Using Available Off-treatment Data

Steps from 1 to N are similar to the ones already described for continuous endpoints (see section 7.3.1.2.2), while Steps N+1 and N+2 are as follows:

- **Step N+1 – Analysis**: Responder subjects will be derived in each of the 1000 complete imputed datasets derived from Step N.2 (i.e., a subject is responder if change from baseline ≥ 100 mL, otherwise non-responder). The proportion of responder subjects will be analyzed in each of the 1000 complete imputed datasets with a Logistic Regression Model including treatment, region and prior asthma therapy as factors and baseline value as covariate using PROC GENMOD.

- **Step N+2 – Combine the Results**: Results derived from Step N+1 will be combined using Rubin's rule. The Rubin's rule will be applied to the log odds ratios (estimates and their standard error). As last step, the final combined estimation using Rubin's rule will be back-transformed (i.e., exponential transformation) in order to obtain a final estimate of the Odds Ratio as well as its 95% CI.

7.3.1.3.2 Imputation of Monotone Missing Data Using Copy Reference (CR) Approach

For CR approach, step 1.1 and step 1.2 are similar to the ones already described for continuous endpoints (see section 7.3.1.2.3) and steps 2 and 3 are as follows:

- **Step 2 – Analysis**: Responder subjects will be derived in each of the 1000 complete imputed datasets derived from Step 1.2 (e.g., a subject is responder if change from baseline ≥ 100 mL, otherwise non-responder). The proportion of responder subjects will be analyzed in each of the 1000 complete imputed datasets with a Logistic Regression Model including treatment, region and prior asthma therapy as factors and baseline value as covariate using PROC GENMOD.
- **Step 3 – Combine the Results**: Results derived from Step 2 will be combined using Rubin's rule. The Rubin's rule will be applied to the log odds ratios (estimates and their standard error). As last step, the final combined estimation using Rubin's rule will be back-transformed (i.e., exponential transformation) in order to obtain a final estimate of the Odds Ratio as well as its 95% CI.

7.3.2 Handling of Missing or Incomplete Dates

Smoking

Unless otherwise stated, imputation rules for missing or partial start/stop dates of smoking are defined below:

For ex-smokers:

- If start YEAR is missing, then no imputation will be done, and the duration of smoking will not be calculated.
- If start YEAR is not missing and MONTH is missing, then January 1st will be assumed (01JANYYYY).
- If only start DAY is missing, then first day of month will be assumed (01MMMYYYY).
- If the stop YEAR is missing, then no imputation will be done, and the duration of smoking will not be calculated.
- If the stop YEAR is not missing and the stop MONTH is missing, then December 31st will be assumed (31DECYYYY).
- If only stop DAY is missing, then last day of the month will be assumed.
- If the stop date imputed based on the above rules is after the date of informed consent, then the date of informed consent will be assumed as stop date.

Medications and Procedures

The medications will be allocated to the first category allowed by the available data, according to the following order:

1. Concomitant medication;
2. Post-treatment medication;
3. Previous medication.

In case of missing or incomplete dates/times not directly allowing allocation to any category of medications/procedures, a worst-case allocation will be done according to the available parts of the start and the stop dates/times.

Adverse Events (AEs) and Asthma Exacerbations

The AE will be allocated to the first category allowed by the available data, according to the following order:

1. Treatment emergent;
2. Post-treatment;
3. Pre-treatment.

In case of missing or incomplete date/time not directly allowing allocation to any of the category of AEs, a worst-case allocation will be done according to the available parts of the start and the stop dates/times.

Date of Last Randomized Study Medication Intake

Unless otherwise stated, imputation rules for missing or partial Date of Last Randomized Study Medication Intake are defined below:

- If the date of the last randomized study medication intake is missing or partial but the intake of at least one dose of the study medication is recorded in the diaries, it will be imputed using the following rules:
  - If completely missing: min (date of last randomized study medication intake in the diaries, date of study completion/ treatment discontinuation);
  - If partially missing: evaluation of partial date of last randomized study medication intake will be performed case by case during DRM and decision will be documented in the DRR.

Asthma Diagnosis

Unless otherwise stated, imputation rules for missing or partial first asthma diagnosis date are defined below:

If the YEAR is missing:

- If the YEAR is missing, then no imputation will be done, and the time since first asthma diagnosis will not be calculated.

If the YEAR is not missing and the MONTH is missing:

- Impute the first diagnosis day as the 1st day of the year (01JANYYYY).

If only DAY is missing:

- Impute the first diagnosis day as 1 (01MMMYYYY).

Asthma History: Last Documented Asthma Exacerbation

Unless otherwise stated, imputation rules for missing or partial last documented asthma exacerbation date are defined below:

If the YEAR is missing:

- If the YEAR is missing, then no imputation will be done, and the time since last documented asthma exacerbation will not be calculated.

If the YEAR is not missing and the MONTH is missing:

- Impute the last documented asthma exacerbation day/month as the 1st day of the year (01JANYYYY).

If only DAY is missing:

- Impute the last documented asthma exacerbation day as 1 (01MMMYYYY).

Treatment taken for an Asthma Exacerbation

For the calculation of the duration of the treatment taken for an asthma exacerbation, the following rules will be applied.

Missing or partial start date:

- In case of completely missing treatment start date, the exacerbation start date will be considered as the treatment start date;
- In case of partial treatment start date, the imputation will be performed according to the following algorithm:
  1. Impute treatment start date considering the last day of the year/month;
  2. If treatment start date imputed according to step 1 ≤ exacerbation start date, then stop. Else go to step 3;
  3. Impute treatment start date as MAX (treatment start date imputed considering the first day of the year/month, exacerbation start date).

Missing or partial stop date:

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

7.4 Covariates

For continuous endpoints:

Continuous efficacy endpoints (e.g., FEV_1 $AUC_{0\text{-}12h}$ normalized by time) assessed over time will be analyzed, after missing data imputation as per section 7.3.1.2, using an ANCOVA model per each timepoint (i.e., visits or inter-visit periods), including treatment group, region, and prior asthma therapy (derived as defined in section 7.8.9) as fixed effects. The baseline value (e.g., FEV_1 pre-dose at Week 0, for more detail see section 7.8.1) will also be included in the model to be adjusted for.

For dichotomous endpoints:

Dichotomous efficacy endpoints (e.g., pre-dose morning FEV_1 responder) will be analyzed using a logistic regression model including treatment group, region, and prior asthma therapy as fixed effects. The baseline value before dichotomizing, i.e., as continuous variable (e.g., pre-dose morning FEV_1 at Week 0, for more detail see section 7.8.1) will also be included in the model to be adjusted for.

7.5 Interim Analyses

No interim analysis will be performed. One final statistical analysis will be conducted.

7.6 Examinations of Subgroups

The primary and key-secondary efficacy variables will be also analyzed in the overall ITT population stratifying by the subgroups defined below.

1. Age (<65, ≥65) at screening
2. Sex (M, F)
3. BMI (<25, 25-<30, ≥30) at baseline
4. Smoking status of tobacco products (non-smoker, ex-smoker) at screening
5. Pre-bronchodilator FEV_1 predicted at screening (Mild: >65%, Moderate: 50-65%, Severe: <50%)
6. Race (White, Black or African American, Other)
7. Race & ethnicity combined (White/Non-Hispanic, Black/Non-Hispanic, Hispanic)

No adjustment of the significance level for testing will be made, since all these subgroup analyses will be considered exploratory and may only be supportive of the analyses of the primary and key-secondary variables.
For each subgroup, the mean difference between treatments and its corresponding 95% CI will be estimated according to the model for the main estimand as described in section 9.1.1.1 and section 9.2.1.1.1. These estimates will be presented on a forest plot, along with the results of the main analysis of the corresponding variable.
If there are too few subjects available for a meaningful analysis of a particular subgroup (i.e., it is not considered appropriate to present analyses where there are less than 20 subjects per category of subgroup), the efficacy variables will not be formally analyzed in that subgroup. In this case, only descriptive summaries will be provided.

7.7 Descriptive Statistics

For quantitative variables descriptive statistics will include the n (the number of non-missing values), the mean, the standard deviation (SD), the median, the minimum (min) and the maximum values (max). The count of missing observations will be provided in all descriptive tables.

For categorical variables, the number (n) and percentage (%) of subjects with a specific level of the variable will be presented. The number of missing values will be displayed as a "Missing" category, where appropriate. Unless otherwise specified, the denominator for each percentage will be the number of non-missing observations within the analysis set.

7.8 Definitions

7.8.1 Change from Baseline and Baseline Values

The change from baseline is defined as:

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

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

Variables	Baseline value
• FEV_1 $AUC_{0\text{-}12h}$ • Peak FEV_1 within the first 3 hours post dosing • Trough FEV_1 • Pre-dose morning FEV_1 • FEV_1 response	The baseline value is the arithmetic mean of the pre-dose FEV_1 measurements (at 45 mins and 15 mins pre-dose) collected at week 0 (Visit 2). If one of the two pre-dose values is missing, the baseline will be equal to the available pre-dose value. Otherwise, in case of both pre-dose measurements missing the baseline value will be considered as missing.
• Morning PEF	The derived morning "Best PEF" for the statistical analysis will be calculated for each morning eDiary session as the highest morning PEF value in the range [50-900] L/min among all the pre-dose PEF measurements available in that eDiary session. The derived morning "Best PEF" for the statistical analysis will be calculated only for morning eDiary sessions with at least two pre-dose PEF measurements available. Baseline for morning PEF will be calculated as the arithmetic mean of all derived morning "Best PEF" values from the morning eDiary session of the day after Visit 1 to the morning eDiary session of the day of Visit 2 (inclusive). The baseline will be calculated if at least 7 derived morning "Best PEF" values will be available during the run-in period.

Variables	Baseline value
• Evening PEF	The derived evening "Best PEF" for the statistical analysis will be calculated for each evening eDiary session as the highest evening PEF value in the range [50-900] L/min among all the pre-dose PEF measurements available in that eDiary session. The derived evening "Best PEF" for the statistical analysis will be calculated only for evening eDiary sessions with at least two pre-dose PEF measurements available. Baseline for evening PEF will be calculated as the arithmetic mean of all derived evening "Best PEF" values from the evening eDiary session of the day of Visit 1 to the evening eDiary session of the day before Visit 2 (inclusive). The baseline will be calculated if at least 7 derived evening "Best PEF" values will be available during the run-in period.
• ACQ-5 and ACQ-7 score	The baseline value is the ACQ-5 and ACQ-7 total score recorded at week 0 (Visit 2). In case of multiple assessments at week 0 (Visit 2), the baseline will be the last ACQ-5 and ACQ-7 total score recorded before drug administration.
• Rescue medication-free days	The baseline value is the percentage of days with no rescue medication (i.e., day with a sum of puffs of rescue medication = 0) collected during the run-in period, derived as: (number of days with no rescue medication during the run-in period / number of days on which daily rescue medication use is assessed during the run-in period)*100. The eDiary sessions to be considered for the run-in are from the evening of the first day of the run-in, until the morning of the day after the last day of the run-in period. The baseline value is set to missing if there will be fewer than 7 daily entries in the run-in period. For each day, the "daily use of rescue medication" will be calculated as the sum of the number of puffs taken during the day (recorded in the evening eDiary session of the day) and taken during the night (recorded in the morning eDiary session of the subsequent day). If one of these two eDiary sessions (evening or morning) associated with the day is missing, the daily use of rescue medication in that day will be considered as missing.

Variables	Baseline value
• Asthma symptom-free days	The baseline value is the percentage of days with no asthma symptom (i.e., total daily asthma symptom score = 0) collected during the run-in period, derived as: (number of days with total daily asthma symptom score = 0 during the run-in period / number of days on which daily asthma symptom is assessed during the run-in period)*100. The eDiary sessions to be considered for the run-in period are from the evening of the first day, until the morning of the day after the last day of the run-in period. The baseline value is set to missing if there were fewer than 7 diary entries in the run-in period. For each day of run-in period, the "total daily asthma symptoms score" will be calculated as the mean of the 8 scores (i.e., 4 symptoms scores: cough, wheezing, chest tightness and breathlessness, collected in the evening eDiary session of the day and 4 symptoms scores collected in the morning eDiary session of the subsequent day). If one of these two eDiary sessions (evening or morning) associated with the day is missing, the total daily asthma symptom score will be considered as missing.
• Pre-dose FVC	The baseline value is the average of the FVC measurements (L) at -45min and -15min collected at Week 0 (Visit 2). If one of the two pre-dose values is missing, the baseline will be equal to the available pre-dose value.
• Vital signs parameters	The baseline value is the pre-dose measurement at Visit 2 (week 0). If missing, the baseline will be equal to the last available value collected at any visit (schedules or unscheduled) before Visit 2. Otherwise, will be missing.
• 12-lead ECG parameters	The baseline value is the pre-dose measurement at Visit 2 (Week 0). If missing, the baseline will be equal to the last available value collected at any visit (schedules or unscheduled) before Visit 2. Otherwise, will be missing.
• Hematology and blood chemistry parameters	The baseline value is the measurement at Visit 2 (if collected). If missing, the baseline will be equal to the last assessment value collected at any visit (schedules or unscheduled) before Visit 2. Otherwise, will be missing.

7.8.2 Date of First and Last Randomized Study Medication Intake

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

The date of last randomized study medication intake is the one recorded in the Study Termination form of the eCRF, corresponding to the date part of the variable RFENDTC in the SDTM dataset DM.

7.8.3 Visit Dates

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

For inter-visit derivation (see section 7.10), if SVENDTC > SVSTDTC, SVSTDTC will be used to define the last visit date.

7.8.4 Date of Start of Randomized Treatment Period

The date of start of randomized treatment period is defined as the date of the first randomized study medication intake within the study, of CHF 1535 pMDI 800/24 µg (Test Treatment) or CHF 718 pMDI 800 µg (Reference Treatment).

7.8.5 Date of End of Efficacy Assessment Period/Discontinuation

The date of end of efficacy assessment period/discontinuation is defined as:

- The date of Visit 5 (SVSTDTC) if available.
- Otherwise as the date of ETD visit (SVSTDTC) if available and if at this visit, the subject did not accept to continue attending study visits according to the schedule (answer is NO to the question “Has the patient accepted to attend post treatment visits?” in “Study Termination - Treatment Discontinuation” form).
- Otherwise as the “Date of study discontinuation” as reported in the “Study Termination (post-treatment period) – Early Withdrawal” form, if the subject accepted to continue attending study visits according to the schedule.
- Otherwise as the “Date of study discontinuation” as reported in the “Study Termination - Treatment Discontinuation” form.

7.8.6 On-treatment and Off-treatment Periods

- The on-treatment period is defined as the period between the date of first randomized study medication intake and the date of last randomized study medication intake.

- On-treatment data are defined as the data collected during the on-treatment period. On the day of first randomized study medication intake, only the data collected after the first dose of the randomized study medication will be considered as collected on-treatment.

- The off-treatment period, in case subject attends post-treatment visits, is defined as the period between the day after the date of last randomized study medication intake and the date of End of Efficacy Period/date of subject withdrawal from the study (extremes included).

- Off-treatment data are defined as the data collected during the off-treatment period.

7.8.7 Study Day

For the e-Diary data, the study day will be calculated as:

- (date of the day – date of start of randomized treatment period +1).

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

- Date of event – date of first randomized study medication intake + 1 (if date of event ≥ date of first randomized study medication intake);

or

- Date of event – date of first randomized study medication intake (if date of event < date of first randomized study medication intake).

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

- For TEAEs:
  - AE onset date – date of first randomized study medication intake +1 (if AE onset date is completely known);
  - missing (if AE onset date is incomplete or unknown).

7.8.8 Duration of Adverse Events or Medications

The duration of an AE or medication will be calculated as follows:

- End date – Start date + 1 (when both dates are completely known).
- Date of study completion/discontinuation – Start date + 1 (when the start date is fully known but the AE or medication still ongoing at the end of the trial): in this case the duration will be presented as ">x" days in the listing rather than "x" days.
- Missing (when the start date is incomplete or unknown, or when the AE or medication ended but with an incomplete or unknown end date, or when the start date is greater than date of study completion/discontinuation).

7.8.9 Prior Asthma Therapy

Prior asthma therapy is recorded in IWRS and eCRF. In this document, prior asthma therapy refers to the data collected in eCRF, which will be used e.g., for summary statistics or analysis models.
In analysis model will be included the following categories: Medium Dose ICS, Medium Dose ICS/LABA (aggregated from categories 'ICS+LABA free combo' and 'ICS/LABA fixed combo') and High Dose ICS.

7.9 e-Diary Data

Data recorded in the e-Diary will be included for the calculation of compliance and, in general, in the diary derived variables, following the derivation rules as explained in section 8.6 and 9.2.2.

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

7.10 Data Re-allocation

- In general, for by-visit (or time point) summaries, data recorded at the scheduled visit (or scheduled time point) will be presented. Data collected at unscheduled visits/time points will be reviewed at the Data Review Meeting (DRM) prior to database lock. Any re-allocation of unscheduled data will be described and justified in the Data Review Report (DRR), which will be finalized prior to database lock. Listings will include scheduled, unscheduled, and early discontinuation data.
- As a general rule for all the assessments related to demographics data performed more than once during the screening period, the last available data will be used as demographic variable.
- **For subjects who discontinue from the study, data collected in a single visit after baseline** (i.e., Hematology and Blood Chemistry parameters) **and recorded at the Early Treatment Discontinuation Visit (ETDV)** will be re-allocated to the expected visit if performed +/- 14 days from the expected date according to the scheduled-of-assessment (i.e., visit 5 for Hematology and Blood Chemistry parameters).
- **For subjects who discontinue from the study, data collected at multiple visits** (e.g., Spirometry) **and recorded at the Early Treatment Discontinuation Visit (ETDV)** will be re-allocated according to the following rules:
    - If the ETDV was performed less than 2 days after the preceding visit, data recorded at the ETDV will not be re-allocated and they will be excluded from the statistical analysis;
    - Otherwise, select the planned theoretical visit (as per flow chart) following the last one performed before the ETDV with the expected theoretical date closest to the date of the ETDV and
        - If the appropriate visit, identified in the steps above, was performed by the subject (as he/she accepted to continue attending study visits according to the schedule after treatment discontinuation), data recorded at the ETDV will not be re-allocated to the planned theoretical visit.
        - If the ETDV is equidistant between two planned theoretical visits, the data recorded at the ETDV will be re-allocated to the latest of the two possible planned theoretical visits.
        - Otherwise, the data recorded at the ETDV will be re-allocated to the planned theorical date closets to the date of the ETDV.

      For each assessment, only the visits at which the assessment is scheduled (as per flow chart) will be considered for re-allocation.
- **For subjects who discontinue from the study, efficacy data recorded in the eDiary from the last study visit performed before the date of study discontinuation onwards**

will be re-allocated to the next expected inter-visit period (e.g., if a subject discontinues the study between Visits 3 and 4, then the efficacy eDiary data collected between Visit 3 and the study discontinuation date will be re-allocated to the inter-visit period Visit 3-Visit 4).

- **For subjects who discontinue from the study treatment or discontinue from the study, study medication intake data recorded in the eDiary from the last study visit performed before the date of last randomized of study medication intake onwards** will be re-allocated to the next expected inter-visit period (e.g., if a subject discontinues the study treatment or the discontinues the study between Visits 3 and 4, then the study medication intake data collected between Visit 3 and the study treatment / study discontinuation date will be re-allocated to the inter-visit period Visit 3-Visit 4).
- Reallocation of data collected in the eDiary to inter-visit periods:

  In case of missing intermediate study visit not due to the re-allocation of data collected at the early termination visit (e.g., Visit 4 missing, but Visits 3 and 5 performed), the expected date for the missing intermediate visit (e.g. Visit 4) will be derived through the following algorithm:

  - If Visit 3 is missing, then derived Visit 3 Date = Visit 2 Date + 28 days.
  - If Visit 4 is missing, then derived Visit 4 Date = Visit 2 Date + 56 days.

  For subjects who discontinue from the study with early termination visit available, missing intermediate study visits might result after re-allocation of the early termination visit (e.g., Visit 3 is the last Visit performed, Visit 4 missing, Visits 5 available as a result of the re-allocation of the ETV. See above "Data collected at multiple visits"). In these cases, the expected date for the missing intermediate study visits and the resulting inter-visit periods will be derived through the same algorithm reported above (e.g., in the example above, considering Visit 3 date and the date of the re-allocated Visit 5). Study medication intake data recorded in the eDiary from the last study visit performed before the date of last randomized study medication intake onwards will be reallocated on the basis of the inter-visit periods defined above.

  For subjects who discontinue from the study with no early termination visit available, eDiary data recorded from the last study visit performed onwards will be reallocated to the next expected inter-visit period.
- For spirometry, if the re-scheduled Visit 1 is done for the assessments of eligibility, this assessment will be used for the analysis at Visit 1.
- The following general rules to handle unscheduled assessments during the efficacy assessment period (i.e., from Visit 2 to Visit 5) will be considered:
  - 12-lead ECG:
    - the unscheduled assessment will be considered associated to the nearest expected time point, or the first expected time point in case of equal distance, taking into account the unscheduled time point relative to the time of medication intake and the specified time windows. Once the unscheduled assessments are allocated, for the multiple measurements associated to the same time point the arithmetic mean will be calculated for HR, QTcF, PR and QRS.

Expected time point	LL (excluding)	UL (including)

Pre-dose	…	<0
30 min post-dose	>0 min post-dose	45 min post-dose
1 h post-dose	45 min post-dose	2h 30 min post-dose
4 h post-dose	2h 30min post-dose	8h post-dose
12h post-dose	8 h post-dose	…

- Vital signs:
  - the unscheduled assessment will be considered associated to the nearest expected time point, or the first expected time point in case of equal distance, taking into account the unscheduled time point relative to the time of medication intake and the specified time windows. Once the unscheduled assessments are allocated, for the multiple measurements associated to the same time point the arithmetic mean will be calculated for systolic and diastolic blood pressures.

Expected time point	LL (excluding)	UL (including)
Pre-dose	…	<0
30 min post-dose	>0 min post-dose	45 min post-dose
1 h post-dose	45 min post-dose	2h 30 min post-dose
4 h post-dose	2h 30min post-dose	8h post-dose
12h post-dose	8 h post-dose	…

- Lab parameter:
  - the unscheduled assessment will be considered associated to the nearest expected time point, or the first expected time point in case of equal distance, taking into account the unscheduled time point relative to the time of medication intake and the specified time windows. Once the unscheduled assessments are allocated, for the multiple measurements associated to the same time point the arithmetic mean will be considered for standard hematology and blood chemistry parameter.
- Spirometry (only for FEV1 and FVC):
  - the unscheduled assessment will be considered associated to the nearest expected time point, or the first expected time point in case of equal distance, taking into account the unscheduled time point relative to the time of medication intake and the specified time windows. Once the unscheduled assessments are allocated, for the multiple measurements associated to the same time point the highest value from the measurements (regardless of the spirometry QC grade) will be considered for FEV1 and FVC. In case of equal values, the closest to the expected time point will be considered. Windows for nearest expected time point:

Expected/scheduled time point	Lower limit (excluding)	Upper limit (including)
-45 min pre-dose	…	-30
-15 min pre-dose	-30 min	< 0 min (before dosing)

5 min post-dose	> 0 min (after dosing time)	10 min
15 min post-dose	10 min	22 min 30 sec
30 min post-dose	22 min 30 sec	45 min
1 h post-dose	45 min	1h 30 min
2 h post-dose	1h 30 min	2h 30 min
3 h post-dose	2h 30 min	4h 30 min
6 h post-dose	4h 30 min	7h 30 min
9 h post-dose	7h 30 min	10h 15 min
11h 30min post-dose	10h 15 min	11h 45min
12h post-dose	11h 45 min	…

For all visits, if unscheduled is done to check the eligibility or the reason for the unscheduled assessments is that the planned visit assessment is invalid, then the unscheduled assessment should be used in the analysis.

Potential issues of the approach above defined, other decisions regarding data re-allocation and the handling of unscheduled/optional assessments will be evaluated during the DRM and documented in the DRR.

Note: All the calculations for analyses (descriptive and inferential) will be done after this re-allocation of data.

7.11 Exclusion of Data from the Statistical Analyses

7.11.1 Exclusion of Data from All Statistical Analyses

Lung Function parameters

All lung function parameters value not rejected by the Investigator will be considered in the statistical analysis, even those classified as "Unacceptable" by the over-reader. This follows the approach recommended by the paper by Hankinson et al. [7], where it was concluded that quality assessment regarding the acceptability of individual blows should be primarily used as an aid to assess good quality during testing rather than a reason to subsequently disregard data.

If inclusion criteria #5 or #6 were not met at Visit 1 and the spirometry was repeated before Visit 2, the 2nd assessment (i.e., the one repeated before Visit 2) will be considered as the Visit 1 assessment in all the analyses. In this case, data originally recorded at Visit 1 will be excluded from the analysis.

eDiary Data

The data recorded in the eDiary before Visit 1 or after the date of end of efficacy assessment period/ discontinuation will not be considered in the calculation of the study treatment compliance. If "date of end of efficacy assessment period/ discontinuation" = "Date of Visit 5", the evening session of this date, if present, will also be discarded in the calculation of compliance, efficacy and, in general, the diary derived variables. For any other condition (any other visit, including Early Termination Visit / discontinuation) the evening session of the date of end of efficacy assessment period/ discontinuation, if present, should be included.

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

PEF Data

The following sessions will not be included for the analysis of PEF parameters:

- The sessions with only 1 pre-dose PEF measurement available.
- The sessions with at least two pre-dose PEF measurements available, but with only one measurement in the range [50-900] L/min. PEF values outside this range are not reliable since physiologically not possible for the study subject population and will be most likely due to poor subject technique or flow-head fault.

12-lead ECG numerical parameters:

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

- Subjects with a pacemaker inserted before study entry will be identified by the presence of at least one of the following preferred terms in the medical/surgical history or concomitant diseases: “Cardiac pacemaker adjustment”, “Cardiac pacemaker evaluation”, “Cardiac pacemaker insertion” , “Cardiac pacemaker removal”,, “Cardiac pacemaker replacement”, “Diaphragmatic pacemaker insertion”, “Electrocardiogram pacemaker spike”, “Pacemaker generated arrhythmia”, “Pacemaker generated rhythm”, “Pacemaker syndrome”, “Wandering pacemaker”, “Cardiac assistance device user”, “Cardiac complication associated with device”, “Cardiac device reprogramming”, “Cardiac resynchronisation therapy”, or any other terms that include “Pacemaker”.
- Subjects with permanent atrial fibrillation will be identified by the presence of the following preferred term in the concomitant diseases: “Atrial fibrillation”.

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

Regarding the 12-lead ECG, it should be highlighted that the rules above defined will apply only to numerical parameters (HR, QTcF, PR and QRS), while no exclusion of data on abnormalities for investigator’s interpretation will be performed (e.g., in case of atrial fibrillation, the occurrence of this abnormality will be considered in the statistical analysis, while the numerical parameters measured at the same time point will be excluded).

In case of data excluded from the statistical analysis (in all situations above described in this paragraph but also in other cases, for example: lung function tests excluded due to technical issues, data excluded due to ETDV performed and data not re-allocated due to subject staying in the study), the derived variables based on these data will not be calculated. For example, the change from baseline to Visit 5 will not be calculated if the measurement at Visit 5 is excluded from the statistical analysis, or all the changes from baseline will not be calculated if the measurement at baseline is excluded.

7.11.2 Exclusion of Data from Per Protocol Analyses

No Per-protocol analysis will be performed.

7.12 Listings

All data collected in the eCRF will be presented in the listings on the Randomized set, unless otherwise specified.
Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within participant listings only. All listings will be sorted by participant number, treatment group, investigational site, date/time, and visit. The treatment group as well as participant's sex, age, and race will be presented on each listing.

All the variables derived from the eDiary used in the analyses will be presented in the listings, while the daily eDiary data will not be listed.
All the off-treatment visits and reallocated visits will be flagged in the listings.
Listings will include data as collected, without imputation for missing data.

7.13 Coding

Medical and surgical history, concomitant diseases, procedures, and adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 dated 15 March 2022 or higher.

Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version Global B3 March 2022 or later.

7.14 Other Considerations

7.14.1 Impact of COVID-19 Pandemic

Since this study has been conducted during the COVID-19 pandemic, impact on the scheduled assessments and timing of assessments is expected. Data impacted will be managed as described in the following paragraphs:

- Remote visits: Subjects who replaced clinic visit with remote one will not have the spirometry, and assessments requiring blood collection performed. Spirometry data could be imputed according to the type of analysis done.
- Visit windowing: Remote visits will have the same visit window allowance as regular visits.
- Whether a visit was not done due to COVID-19 will be presented in the listing of study visits. The number of remote visits performed due to COVID-19 will also be summarized by treatment group.
- Whether subjects were diagnosed for COVID-19 will be flagged in all listings. A subject is diagnosed for COVID-19 if the MedDRA preferred term includes the terms 'COVID-19' (the terms 'COVID-19 immunization', 'Post-acute COVID-19 syndrome' are excluded) or 'SARS-COV-2'.
- Whether subjects were vaccinated against COVID-19 will be flagged in the AE and in the prior and concomitant medication listings. A subject is vaccinated for COVID-19 if the verbatim of medications or the indication includes the term 'COVID' and ATC code is 'J07BX'.

The expected amount of missing data due COVID-19 is very limited so no specific rules for missing data are planned.

8 Study Population

8.1 Disposition of Subjects and Discontinuations

8.1.1 Disposition of Subjects

The number of subjects screened (i.e., provided valid written informed consent), the number screen failures and the reasons for screen failure will be presented (overall) using enrolled set.

The number of subjects screened, randomized, randomized and treated, randomized and not treated, who completed / discontinued the study treatment, who completed / discontinued the study will also be presented by region and by site on Randomized set.

The number of subjects who performed each study visit will be summarized for the Randomized set and enrolled set by treatment group and by on- and off-treatment periods.

8.1.2 Discontinuation from the Study and from the Study Treatment

The number and percentage of subjects who:

- Completed the study.
- Withdrew from the study (with reasons of study withdrawal).
- Completed the study treatment.
- Discontinued the study treatment (with reasons for treatment discontinuation).
- Discontinued the study treatment and withdrew the study at the same time (with reasons for treatment discontinuation / study withdrawal).
- Discontinued the study treatment (with reasons for treatment discontinuation), continuing the study and completed all the planned the study visits.
- Discontinued the study treatment (with reasons for treatment discontinuation), continuing the study and did not complete all the planned the study visits.

Will be presented by treatment group and overall using the Randomized set.

Time to discontinuation from the study treatment and time to discontinuation from the study after randomization will be analyzed using the Kaplan-Meier method for the Randomized set.

Notes:

- Time to discontinuation from the study (weeks) = (date of study completion/discontinuation – date of start of randomized treatment period + 1) / 7.
- Time to discontinuation from the study treatment (weeks) = (date of study treatment completion/discontinuation – date of start of randomized treatment period + 1) / 7.
- Time to discontinuation from the study (weeks) or from the study treatment (weeks) = 0, if subject randomized but not treated.
- The analysis of time to discontinuation from the study includes also subjects who discontinued from the study treatment but remain in the study. Those subjects will be assigned to the randomized treatment arm.

In the Kaplan-Meier analysis of time to discontinuation (from the study and from the study treatment), subjects who complete the study/treatment will be censored at the date of completion. For the study periods [0-4) weeks, [4-8) weeks, [8-12) weeks, the number of subjects in study at the beginning of the period, the cumulative number of subjects who discontinue (from the study and from the study treatment) at the end of period and the probability of discontinuation (from the study and from the study treatment) at the end of period.
The KM Plot of time to study discontinuation (from the study and from the study treatment) by treatment group will also be presented.

8.1.3 Protocol Deviations and Analysis Sets

Deviations will be classified according to the following categories:

- Concomitant Medication.
- Discontinuation.
- Inclusion/Exclusion Criteria.
- Informed Consent.
- Safety Reporting.
- Study Intervention.
- Trial Procedures.

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

Important protocol deviations will be summarized by treatment using the ITT Set.

The number of subjects included in each of the ITT and Safety Sets will be summarized for each treatment and overall using the Randomized Set.

8.2 Demographic and Baseline Characteristics

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

8.2.1 Demographic Characteristics

Demographics and baseline variables will be summarized by treatment group and overall using descriptive statistics for the ITT set and repeated on Safety set (if different). These will include age, age categories, gender, race, height and weight at baseline and body mass index (BMI).

Notes:

- Age categories: <65 years; ≥ 65 years (all categories to be displayed even if 0 subject).
- Height and weight at baseline [if available, otherwise at screening] will be presented.
- Baseline BMI will be calculated as weight (kg) / height (m2), if weight available at baseline; otherwise, BMI collected in eCRF at screening will be used.

8.2.2 Asthma History

Asthma history collected at Screening will be summarized by treatment group and overall on the ITT set and repeated on Safety set (if different):

- Time since first diagnosis (months).
- Asthma medication category at study entry [ICS/LABA combination (i.e., ICS/LABA fixed combination, ICS + LABA free combination), high dose ICS and medium dose ICS].
- Number of asthma exacerbation in the 4 weeks before screening (summary of actual exacerbations number and by category: 0 or 1+).
- Time since last documented exacerbation
- Treatment of the most recent exacerbation (Systemic Corticosteroid, Hospitalization, Emergency Room).

Note:

- Time since first diagnosis (months) = (Screening date – First diagnosis date + 1) /30.4375.
- Time since last documented exacerbation (months) = (Date of Visit 1 – Date of last exacerbation) / 30.4375. Note: the date of last exacerbation will be "Date of the exacerbation ended" or "Date of the most recent exacerbation ended" (i.e., variable name MHENDTC) from the eCRF page "Asthma History".

8.2.3 Smoking Status

For tobacco products, smoking status (Non-smoker or Ex-smoker or Current smoker), duration of smoking (years), and number of pack-years recorded at screening will be presented by treatment group and overall on the ITT set and repeated on Safety set (if different).

For electronic cigarettes, smoking status (Non-smoker or Ex-smoker or Current smoker), duration of smoking (years), and type of e-Cigarettes (Nicotine based or Not nicotine based) recorded at screening will be presented by treatment group and overall on the ITT set and repeated on Safety set (if different).

Notes:

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

8.2.4 Spirometry and Reversibility Test

Pre-bronchodilator and post-bronchodilator FEV_1, FVC, FEV_1 predicted (%) Reversibility FEV_1 and Reversibility FEV_1 (%) post-bronchodilator at Screening (collected during Clinic Visit – after reallocation if any inclusion criteria is not met) and FEV_1 and FVC at Visit 2 pre-dose (see section 7.8.1 for details) will be summarized by treatment group and overall for the ITT set and repeated on Safety set (if different).

8.2.5 Rescue Medication Use During Run-in Period

Use of rescue medication during run-in period will be summarized using descriptive statistics for the percentage of rescue medication-free days on the ITT set.

Data recorded from the evening eDiary session of the day of the Visit 1 to the morning eDiary session of the day of the start of randomized treatment period (i.e., Visit 2) will be considered

as data from the run-in period (if at least 7 daily use of rescue medication are available – see section 7.8.1).

Notes:

- Percentage of rescue medication-free days = 100 * (number of days with no rescue medication days during run-in period / number of days on which daily rescue medication use is assessed during the run-in period).

A rescue medication-free day is a day with a sum of puffs of rescue medication = 0. Summary will be presented on the ITT set and repeated on Safety set (if different).

8.2.6 Others Baseline Characteristics

All others characteristic (e.g., ACQ-5, ACQ-7) collected at screening or at Visit 2 (before first study treatment intake) will be described directly in the summary statistics presented in the efficacy analyses section 9.

8.3 Medical History and Concomitant Diseases

Medical/surgical history and concomitant diseases will be summarized by system organ class (SOC) and preferred term (PT), by treatment group and overall using the ITT set and repeated on Safety set (if different).

Notes:

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

8.4 Medications

Previous medications, concomitant medications and post-treatment medications will be summarized by treatment group on the ITT set through frequency distributions and percentages by Anatomical Main Group (1st level of the ATC classification), Therapeutic Subgroup (2nd level of the ATC classification), Chemical Subgroup (4th level of the ATC classification) and preferred name.

Subjects experiencing more than one medication classified in the same category (previous medications, concomitant medications, and post-treatment medication) within the same anatomical main group, therapeutic subgroups, chemical subgroup, and preferred name will be counted only once.

The medications will be classified according to the following rules:

- Previous medication: start date < date of first randomized study medication intake and stop date ≤ date of first randomized study medication intake;
- Concomitant medication: start date < date of last randomized study medication intake and stop date ≥ date of first randomized study medication intake or ongoing (if ongoing, the subject should have the first randomized study medication intake date non-missing);
- Post-treatment medication: start date ≥ date of last randomized study medication intake.

Asthma medication will be identified using the Indication ticked to "Asthma" or "Asthma Exacerbation" in the Prior and Concomitant Medications eCRF page.

A full review of the medications to identify any medication taken for asthma (but not linked to an Asthma medication with the tick box) will be performed during the DRM.

The following tables will be provided:

- Previous medications:
  - Asthma medications (Prior and Concomitant Medications eCRF page);
  - Non- Asthma medications (Prior and Concomitant Medications eCRF page).
- Concomitant medications:
  - Asthma medications (Prior and Concomitant Medications eCRF page);
  - Non- Asthma medications (Prior and Concomitant Medications eCRF page).
- Post-treatment medications:
  - Asthma medications (Prior and Concomitant Medications eCRF page);
  - Non- Asthma medications (Prior and Concomitant Medications eCRF page).

In case of missing or incomplete dates not directly allowing allocation to any of the three categories of medications (i.e., previous medications, concomitant medications, post-treatment medications), see the rules defined in section 7.3.

8.5 Procedures

Treatment group will summarize prior procedures, concomitant procedures and post-treatment procedures on the ITT set through frequency distributions and percentages by SOC and PT.

The procedures will be classified according to the following rules:

- Prior procedures: start date < date of first randomized study medication intake and end date ≤ date of first randomized study medication intake;
- Concomitant procedures: start date < date of last randomized study medication intake and stop date ≥ date of first randomized study medication intake or ongoing (if ongoing, the subject should have the first randomized study medication intake date non-missing);
- Post-treatment procedures: start date ≥ date of last randomized study medication intake.

In case of missing or incomplete dates not directly allowing allocation to any of the four categories of procedures, see the rules defined in section 7.3.

8.6 Compliance

Run-in medication compliance (recorded as run-in medication in the eDiary) and study treatment compliance (recorded as study medication in the eDiary) will be evaluated based on the information recorded twice daily by the subject on the eDiary and the information recorded in the eCRF during Clinic visits.

If for a dosing time point both diary and eCRF data are available (e.g., for the morning dose of the randomized study medication on the days of the scheduled clinic visits), only the eCRF data will be considered.

In case of subjects with an incorrect setting of electronic eDiary at randomization (run-in questions asked during the randomized treatment period or vice versa), since in Visit 2 (week 0) the run-in medication is required to be brought by the patient back to the site and the study drug is dispensed, compliance will be calculated using the number of inhalations recorded in the questionnaire regardless the setting of electronic eDiary; thus, in case of subjects with an incorrect setting of electronic diary at randomization (run in questions asked during the randomized treatment period or viceversa) it is assumed that the subject took the appropriate medication available (i.e., run-in medication during run-in period or study drug during study treatment period).
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8.6.1 Treatment Compliance

8.6.1.1 Treatment Compliance During Run-In period

Treatment compliance during the Run-in Period (CHF 718 pMDI 100µg) will be evaluated based on the information recorded daily by the subject on the eDiary and the information recorded in the eCRF during Clinic visits. Treatment compliance will be summarized on ITT set.

Treatment compliance is calculated as:

Treatment compliance = [(Total number of administered doses) / (Total number of scheduled doses)] * 100

The total number of administered doses will be calculated as the total number of inhalations recorded from the evening eDiary session of the day of Visit 1 (including morning data collected in eCRF if available) to the morning eDiary session of the day of start of randomized treatment period (reporting the dose taken the evening before), inclusive.

The total number of scheduled doses, since the run-in treatment administration is 2 or 4 inhalations twice daily, will be calculated using the following formula:

Total number of scheduled doses = [(Date of start of randomized treatment period) – (Date of Visit 1)] * x

Where x=4 if the screened subject who was on a medium dose ICS or medium dose ICS-LABA prior to the study was put on CHF 718 pMDI 100μg 2 inhalations BID (TDD 400 μg) during the 2-week run in period OR x=8, if the screened subject who was on a high dose ICS prior to the study was put on CHF 718 pMDI 100μg 4 inhalations BID (TDD 800 μg) during the 2-week run in period.

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

Compliance will be summarized by treatment group.

Treatment compliance will be also categorized as [0%-10%), [10%-20%), [20%-30%), [30%-40%), [40%-50%), [50%-60%), [60%-70%), [70%-80%), [80%-90%), [90%-100%), [100%-

135%], and >135% and <50% vs >=50% and these categories will be summarized by treatment group using frequency distributions and percentages.

8.6.1.2 Treatment Compliance During Treatment Period

Treatment compliance will be evaluated based on the information recorded daily by the subject on the eDiary and the information recorded in the eCRF during Clinic visits. Treatment compliance will be summarized on ITT set.

Treatment compliance is calculated as:

Treatment compliance = [(Total number of administered doses) / (Total number of scheduled doses)] * 100

The total number of administered doses will be calculated as the total number of inhalations performed from the evening eDiary session of the day of first randomized study medication intake (including morning data collected in eCRF if available) to the day of last randomized study medication intake, inclusive.

The total number of scheduled doses will be calculated based on the extent (days) of exposure of each subject.

Notes:

- Extent of exposure (days) = Date of last randomized study medication intake – date of first randomized study medication intake + 1.
- Number of scheduled doses = Extent of exposure (days) * 8 (since the study treatment administration is 4 inhalations twice daily = 8 inhalations).
- If the last day considered in the formula is the date of Visit 5 (Week 12) (i.e., date of last randomized study medication intake = Date of Visit 5), the number of scheduled doses on this day will be 4 (4 inhalations) as study medication will be administered only in the morning (the information on study medication intake on that day will be taken from the eCRF). Therefore, the total number of scheduled doses will be:
  Extent of exposure (days) * 8 – 4.

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

Compliance will be summarized by treatment group.

Treatment compliance will be also categorized as [0%-10%), [10%-20%), [20%-30%), [30%-40%), [40%-50%), [50%-60%), [60%-70%), [70%-80%), [80%-90%), [90%-100%), [100%-135%], and >135% and these categories will be summarized by treatment group using frequency distributions and percentages. In addition, treatment compliance will also be presented for the following categories: <65%, [65% - 135%] and >135%.

8.6.1.3 Treatment Compliance During Inter-Visit Period

Treatment compliance during the inter-visit period is calculated as:

Treatment compliance during inter-visit period = [(Total number of administered doses during the inter-visit period) / (Total number of scheduled doses during inter-visit period)] * 100

- The total number of administers doses during the inter-visit period will be calculated as the total number of inhalations recorded from the first session of the period to the last session of the inter-visit period.

Note that the first session and last session of the inter-visit period will be defined as:

Inter-visit period visit *i* - visit *i* +1 ($2 \leq i \leq 5$) (i.e, Visit 2 – Visit 3, Visit 3 – Visit 4, Visit 4 – Visit 5)	
First session of the period	Last session of the period
• If *i* =2 then first session is the morning session of day of first randomized study medication intake. For instance, the first session of V2-V3 period is the morning session of day of first randomized study medication intake. • Else first session is the morning session of day of Visit *i* (i.e., Visit 3 or Visit 4). For instance, the first session of V3-V4 period is the first session is the morning session of day of Visit 3. Note: we are assuming date of first randomized study medication intake < date of Visit 3.	• If Visit *i* is NOT the last clinic visit performed before the last randomized study medication intake then last session is the evening session of day before Visit *i+1*. For instance, if the last randomized study medication intake is between V4 and V5, V3 is not the last clinic visit performed before the last randomized study medication intake then last session of V3-V4 period is the evening session of day before Visit 4. • Else: o For completed subjects: last session is the study medication intake recorded at morning session of day of Visit 5. For instance, if V5 occurs, the last session of the V4-V5 period is the study medication intake recorded at morning session of day of Visit 5. o For discontinued subjects: last session is the last session of the day of study medication intake. For instance, if subject discontinued between V3 and V4, last session of V3-V4 period is the last session of the day of study medication intake.

Of note, all the definitions included in the table above and used in this section are expressed in terms of planned sessions. For example, the first session to be considered in inter-visit period Visit 3 – Visit 4 will be always the morning session of the day of first randomized study medication intake, irrespective of the availability of this specific session.

- The <u>total number of scheduled doses</u> will be calculated using the following formula:

  Total number of scheduled doses during inter-visit period =

- if it is NOT the last inter-visit period (i.e., not Visit 4 – Visit 5), then
  = Extent of Exposure during inter-visit period (days)* 8 (4 inhalations b.i.d = 8 inhalations);
- if the last day considered in the formula is not the date of Visit 5 (date of last study medication intake ≠ Date of Visit 5), then
  = [Extent of Exposure during inter-visit period (days) + 1] * 8 (4 inhalations b.i.d = 8 inhalations);
- otherwise,
  = Extent of Exposure during inter-visit period (days)* 8 (2 inhalations b.i.d = 4 inhalations) + 4 inhalations,

Being the Extent of Exposure during each inter-visit period (days) = date of the last session of the inter-visit period – date of first session of the inter-visit period .

For subjects with date of discontinuation equal to the date of Visit 2, then for the inter-visit period Visit 2 – Visit 3, it will be consider:

- treatment exposure = 1 day;
- # scheduled doses = 8 (4 inhalations b.i.d = 8 inhalations);

8.6.2 Diary Compliance

Diary will be considered as compliant if all expected information is present. Diary compliance will be summarized on ITT set.

8.6.2.1 Diary Compliance During Run-In Period

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

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

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

Compliance to the use of diaries during the run-in period will be summarized by treatment group by means of descriptive statistics. The number and the percentage of subjects in the following categories of compliance will also be presented: [0%-50%), [50%-75%) and [75-100%].

8.6.2.2 Diary Compliance During Treatment Period

Sessions recorded from the evening of the day of start of randomized treatment period to the day of end of efficacy assessment period/discontinuation will be considered for eDiary compliance.

- If date of start of randomized treatment period = date of end of efficacy assessment period or early discontinuation from the study (i.e. no data collecting in the e-diary), compliance will be considered as missing.

- If the day of end of efficacy assessment period or early discontinuation from the study is the day of a clinic visit, the following formula will be used:

  Compliance during the randomized treatment period (%) = [Total number of sessions in the randomized treatment period with data recorded in the diaries / (2*(Date of end of efficacy assessment period or early discontinuation from the study – Date of start of randomized treatment period))]*100.

- Otherwise, the following formula will be used:

  Compliance during the randomized treatment period (%) = [Total number of sessions in the randomized treatment period with data recorded in the diaries / (2*(Date of end of efficacy assessment period or early discontinuation from the study – Date of start of randomized treatment period) + 1)]*100.

Compliance to the use of diaries during the randomized treatment period will be summarized by treatment group by means of descriptive statistics. The number and the percentage of subjects in the following categories of compliance will also be presented: [0%-50%), [50%-75%), [75-100%].

8.6.2.3 Diary Compliance During Inter-Visit Period

eDiary compliance during the inter-visit period is calculated as:

- eDiary compliance during inter-visit period visit i - visit i+1 = [(Total number of sessions with data recorded in the diaries during inter-visit period from the first session of the period to the last session of the inter-visit period visit i - visit i+1) / (Total number of sessions expected during inter-visit period visit i - visit i+1)] * 100

Note that the first session and last session of the inter-visit period will be defined as:

Inter-visit period visit i - visit i+1 ($2 \leq i \leq 5$) (i.e, visit 2 – visit 3, visit 3 – visit 4, visit 4 – visit 5)	
First session of the period	Last session of the period
• If i=2 then first session is the morning session of day of first randomized study medication intake. For instance, the first session of V2-V3 period is the morning session of day of first randomized study medication intake. • Else first session is the morning session of day of visit i (i.e., visit 3 or visit 4). For instance, the first session of V3-V4 period is the first session is the morning session of day of Visit 3. Note: we are assuming date of first randomized study medication intake < date of Visit 3.	• If visit *i* is NOT the last clinic visit performed before the end of efficacy period or early discontinuation from the study, then last session is the evening session of day before visit *i+1*. For instance, if the end of efficacy period or early discontinuation from the study occurs afther V4, V3 is not the last clinic visit performed before the end of efficacy period or early discontinuation from the study then last session of V3-V4 period is the evening session of day before Visit 4. • Else: o For completed subjects: last session is the morning session of day of Visit 5; o For discontinued subjects: last session is the last session of the day of end of efficacy period or early discontinuation from the study.

Of note, all the definitions included in the table above and used in this section are expressed in terms of planned sessions. For example, the first session to be considered in inter-visit period Visit 3 – Visit 4 will be always the morning session of the day of first randomized study medication intake, irrespective of the availability of this specific session.

The total number of sessions expected during inter-visit period visit i - visit i+1 will be calculated using the following formula:

- Total number of sessions expected during inter-visit period visit i - visit i+1 =
    - if visit i - visit i+1 is NOT the last inter-visit period OR if it is the last inter-visit period but not visit 4 - visit 5, then
      = (date of the last session of the inter-visit period – date of first session of the inter-visit period)* 2;
    - if the last inter-visit period is visit 4 - visit 5, then
      = (date of the last session of the inter-visit period – date of first session of the inter-visit period)*2 + 1;
    - otherwise missing

9 Efficacy Analyses

9.1 Primary Efficacy Variable(s)

The primary efficacy analysis and all the sensitivity analyses will be performed using ITT population.

9.1.1 Change from Baseline in FEV_1 $AUC_{0\text{-}12h}$ Normalized by Time at Week 12

9.1.1.1 Main Estimand

The attributes of the main estimand for the primary efficacy endpoint is summarized below:

Target Population	Subjects with included in the ITT Population
Treatments	Randomized study drug (CHF 1535 pMDI 800/24µg vs CHF 718 pMDI 800µg) including rescue medication and any other asthma treatments that may be administered during the study.
Endpoint	Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12.
Intercurrent events	**Early discontinuation from the randomized study drug**: participants will be analyzed irrespective of the occurrence of the event (i.e., targeting a treatment policy strategy). Data collected after discontinuation from the randomized study drug (i.e., off-treatment data) will be included in the analysis.
	Use of not allowed medications and other important protocol deviations: participants will be analyzed irrespective of the occurrence of the event (i.e., targeting a treatment policy strategy). If a subject use of not allowed medications and other important protocol deviations, the data will be used regardless of whether or not the intercurrent event occurs.
	Wrong study drug intake: participants will be analyzed irrespective of the occurrence of the event (i.e., targeting a treatment policy strategy). If a subject takes the wrong study drug, the data will be analyzed as if the intercurrent event had not occurred, thus considering the randomized study drug.
Events leading to missing data	**Missed visit or assessment not performed/not evaluable at intermediate visit:** this kind of event will result in missing data pattern defined as intermittent (i.e., a missing value followed by an observed on-treatment or off-treatment value). These missing data will be imputed under the Missing At Random (MAR) assumption, assuming the data distribution observed on subjects in the same treatment group (hypothetical strategy).

	Early discontinuation from the study: the collected off-treatment data observed on all subjects will be used for the imputation of missing data after study discontinuation for both treatment arms. This approach targets the off-treatment effect that would have been observed if all subjects discontinued from study drug had consented to continue the study. Note: In case of collection of very few off-treatment data such that the planned imputation cannot be performed, the imputation of missing data after study discontinuation will be based on the Copy Reference (CR) approach (i.e., considering the data distribution of the CHF 718 pMDI 800µg TDD arm, including both on-treatment and off-treatment data) as described in section 7.3.1.2.3. This approach targets the reference group effect that would have been observed if all subjects discontinued from study drug had moved to the reference group and consented to continue the study.
Population-level summary	Adjusted treatment difference comparing CHF 1535 pMDI 800/24µg TDD vs. CHF 718 pMDI 800µg TDD.

The primary endpoint is the change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12. The change from baseline will be calculated as described in section 7.8.1.

FEV_1 will be measured at the following time points: -45 min and -15 min pre-dose and 5 min, 15 min, 30 min, 1h, 2h, 3h, 6h, 9h, 11.5h and 12 h post-dose.

The FEV_1 $AUC_{0\text{-}12h}$ will be calculated using the linear trapezoidal method and then normalized to the length of time: $AUC_{0\text{-}12/12h}$, as follows:

$$AUC_{0-12/12h} = \frac{1}{t_{10} - t_0} \sum_{i=1}^{10} \frac{(t_i - t_{i-1})(d_i + d_{i-1})}{2}$$

Where d_i is the spirometry value (FEV_1) obtained at time t_i; t_i is the actual time (in hours) at which d_i is measured. For $t_0 = 0$, d_0 is the mean of the two pre-dose values at baseline or week 12.

FEV_1 $AUC_{0\text{-}12h}$ normalized by time will be assessed at Visit 2 (week 0) and Visit 5 (week 12). Missing data will be imputed as detailed in section 7.3.

The hypothesis to be tested is that CHF 1535 pMDI 800/24µg is superior to CHF 718 pMDI 800µg in the mean change from baseline in FEV_1 $AUC_{0\text{-}12/12h}$ at Week 12.

Off-treatment data will be included in the analysis and a procedure based on multiple imputation techniques will be performed as described in section 7.3.1.2.2 to manage missing data due to study discontinuation. Then, an ANCOVA model including covariates as described in section 7.4 will be performed. In case of issues occurring during the imputation of missing data, missing data due to study discontinuation will be imputed using a CR approach, as described in section 7.3.1.2.3.

From the model, the adjusted means in each group and the difference in adjusted means for the group comparisons will be estimated together with their 95% CIs and p-values (see section 14.1 for SAS code).

Superiority of CHF 1535 pMDI 800/24µg TDD will be demonstrated by a statistically significant difference between treatments (defined as $p<0.05$) favoring CHF 1535 pMDI 800/24µg TDD.

Multiplicity will be taken into consideration as described in section 7.2.

Results will be graphically summarized as follows:

- A figure with adjusted mean change (mean ± 95% CI) from baseline to each study visit by treatment group derived from the ANCOVA model.

Additionally, FEV_1 $AUC_{0\text{-}12h}$ normalized by time at each study visit (actual value and change from baseline) will be summarized by treatment group using descriptive statistics. This descriptive summary will not include imputed data but will include off-treatment data.

9.1.1.2 Sensitivity Analysis of Primary Endpoint Using Main Estimand

As sensitivity analysis, the tipping-point approach to deal with missing data due to early discontinuation from the study will be applied to assess the robustness of the primary analysis approach as described in section 7.3.1.2.4.
As a starting point, delta will vary from -1 L to 0 L with increments of 0.05 L. The increment and the range may be refined based on the analysis results and the location of the tipping point.

9.1.1.3 Sensitivity Analysis of Primary Endpoint, in case of high rate of misclassification of prior asthma therapy

In case of a misclassification rate greater or equal to 10% of prior asthma therapy recorded in IWRS and eCRF, as sensitivity analysis, the same model will be run considering the prior asthma therapy recorded in IWRS as covariate, and not the data recorded in eCRF as specified in section 7.8.9.

9.1.1.4 Sensitivity Analysis of Primary Endpoint, excluding patients randomized more than once with overlapping study periods

In the case of patients randomized more than once who have the first treatment period included in the analysis population overlapped on at least one other treatment period of the same patient, as a sensitivity analysis, the same model will be run excluding those patients from the analysis population.

Treatment periods are defined as overlapping if at least one of the following conditions is met.

- Date of first randomized study medication intake of period X <= the date of first randomized study medication intake of period Y <= Date of last randomized study medication intake of period X

9.2 Secondary Efficacy Variables

9.2.1 Key-Secondary Efficacy Variable

All the analyses and all the sensitivity analyses for key-secondary endpoint will be performed using ITT population.

9.2.1.1 Change from Baseline in Peak FEV_1 Within the First 3 Hours post-dose at Week 12

9.2.1.1.1 Main Estimand

The attributes of the main estimand for the key-secondary efficacy endpoint are the same as described for the primary endpoint (see section 9.1.1.1), except for the endpoint definition:

The key secondary endpoint is change from baseline in peak FEV_1 within the first 3 hours post-dose at Week 12. The change from baseline will be calculated as described in section 7.8.1.

The peak FEV_1 within the first 3 hours post-dose is defined as the highest bronchodilator effect on FEV_1 within the first 3 hours post-dose (i.e., the highest effect/maximum value among the following time points: 5 min, 15 min, 30 min, 1h, 2h, 3h post-dose).

Peak FEV_1 within the first 3 hours post-dose will be assessed at Visit 2 (week 0) and Visit 5 (week 12). Missing data will be imputed as detailed in section 7.3.

The hypothesis to be tested is that CHF 1535 pMDI 800/24µg is superior to CHF 718 pMDI 800µg in the mean change from baseline in peak FEV_1 within the first 3 hours post-dose at Week 12.

The analysis will be performed as described for the primary efficacy variable (see section 9.1.1), and corresponding summaries will be presented.

9.2.1.1.2 Sensitivity Analysis of Key Secondary Endpoint Using Main Estimand

As sensitivity analysis, the tipping-point approach to deal with missing data due to early discontinuation from the study will be applied to assess the robustness of the primary analysis approach as described in section 7.3.1.2.4.
As a starting point, delta will vary from -1 L to 0 L with increments of 0.05 L. The increment and the range may be refined based on the analysis results and the location of the tipping point.

9.2.1.1.3 Sensitivity Analysis of Key Secondary Endpoint in case of high rate of misclassification of prior asthma therapy

In case of a misclassification rate greater or equal to 10% of prior asthma therapy recorded in IWRS and eCRF, as sensitivity analysis, the same model will be run considering the prior asthma therapy recorded in IWRS as covariate, and not the data recorded in eCRF as specified in section 7.8.9.

9.2.1.1.4 Sensitivity Analysis of Key Secondary Endpoint, excluding patients randomized more than once with overlapping study periods

In the case of patients randomized more than once who have the first treatment period included in the analysis population (as described in section 6) overlapped on at least one

other treatment period of the same patient, as a sensitivity analysis, the same model will be run excluding those patients from the analysis population.

Overlapping treatment periods are defined in section 9.2.1.1.4.

9.2.2 Secondary Efficacy Variables

All the analyses for secondary endpoints will be performed using ITT population.

The analyses of secondary efficacy variables are planned to target the same main estimand as described for the primary and key-secondary efficacy endpoints.

Thus, off-treatment data will be included in the analysis and missing data due to study discontinuation will be imputed with a similar approach as described for the primary and key-secondary efficacy variables (see section 7.3.1.2.2). In case of issues occurring during the imputation of missing data, missing data due to study discontinuation will be imputed using a CR approach, as described in section 7.3.1.2.3.

9.2.2.1 Change from Baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 0

Change from baseline in FEV_1 $AUC_{0\text{-}12h}$ normalized by time at Week 0 will be analyzed as described for the primary efficacy variable (see section 9.1.1).

9.2.2.2 Change from Baseline in Peak FEV_1 Within the First 3h Post-dose at Week 0

Change from baseline in peak FEV_1 within the first 3 hours post dose at Week 0 will be analyzed as described for the key-secondary efficacy variable (see section 9.2.1).

9.2.2.3 Change from Baseline in Trough FEV_1 at Week 12

The change from baseline in trough FEV_1 at Week 12 will be calculated as described in section 7.8.1.

Trough FEV_1 is defined as the arithmetic mean of 11.5h and 12h post-dose FEV_1 measurements.

Trough FEV_1 will be assessed at Visit 2 (week 0) and Visit 5 (week 12). Missing data will be imputed as detailed in section 7.3.

The analysis will be performed as described for the primary efficacy variable (see section 9.1.1), and corresponding summaries will be presented.

9.2.2.4 Change from Baseline in Pre-dose Morning FEV_1 at Week 4, 8 and 12

The change from baseline in pre-dose morning FEV_1 at Week 4, 8 and 12 will be calculated as described in section 7.8.1.

Pre-dose morning FEV_1 is defined as the arithmetic mean of the pre-dose FEV_1 measurements (at 45 mins and 15 mins pre-dose). If one of the two pre-dose values is missing, the pre-dose morning FEV_1 will be equal to the available pre-dose value.

Pre-dose morning FEV_1 will be assessed at Visit 2 (week 0), Visit 3 (week 4), Visit 4 (week 8), Visit 5 (week 12). Missing data will be imputed as detailed in section 7.3.

The analysis will be performed as described for the primary efficacy variable (see section 9.1.1), and corresponding summaries will be presented.

9.2.2.5 Change from Baseline in Average Morning PEF Over 12-week Treatment Period

The change from baseline in average morning PEF over 12-week treatment period will be calculated as described in section 7.8.1.

The morning PEF will be collected by the participant on a daily basis.

Variable	Derivation for descriptive analysis	Derivation for inferential analysis
Pre-dose morning best PEF	The **pre-dose morning best PEF** is defined as the highest morning PEF among the available pre-dose morning PEF measurements of that day excluding those listed in section 7.11.1.	See definition on the left side.
Average pre-dose morning PEF at each inter-visit period	The **average pre-dose morning PEF at each inter-visit period** is defined as the arithmetic mean of all the available pre-dose morning best PEF values recorded in each inter-visit period. Availability of at least 7 valid morning sessions per each inter-visit period are required to make the inter-visit period evaluable, otherwise the average morning PEF for that inter-visit period will be set to missing. The **inter-visit period** is defined as the time interval from the morning session of the day after clinic visit to the morning session of the day of next clinic visit (or the date of end of efficacy assessment period/ discontinuation for last inter-visit period). For the first inter-visit period, the date of start of randomized treatment period will be considered as reference point instead of date of Visit 2.	See definition on the left side. Missing average-pre dose morning PEF at inter-visit period will be imputed for each subject discontinuing from the study, according to the strategy defined in section 7.3.1.2, in order to obtain one observed/imputed average-pre dose morning PEF per each of the three inter-visit periods (i.e., [Week 0– Week 4]; [Week 4 – Week 8] and [Week 8 – Week 12]). For the purpose of missing data imputation using off-treatment data, an inter-visit period will be considered: • "on-treatment" if 50% or more of the available pre-dose morning best PEF assessments of the inter-visit period are "on-treatment" assessments; • "off-treatment" if less than 50% of the available pre-dose morning best PEF assessments of the inter-visit period are "on-treatment" assessments.

Variable	Derivation for descriptive analysis	Derivation for inferential analysis
Average pre-dose morning PEF over entire treatment period	The **average pre-dose morning PEF over entire treatment period** is defined as the arithmetic mean of all available pre-dose morning best PEF values recorded all over the entire treatment period. Availability of at least 1 evaluable inter-visit period is required over all treatment period to make the entire treatment period evaluable, otherwise the average morning PEF over entire treatment period will be set to missing. The **entire treatment period** is defined as the time interval from the morning session of the day after the date of start of randomized treatment period to the morning session of the date of end of efficacy assessment period/ discontinuation.	The **average pre-dose morning PEF over entire treatment period** is defined as the arithmetic mean of the three observed/imputed averages pre-dose morning PEF at inter-visit periods.

Average pre-dose morning PEF will be calculated at baseline (i.e., average of the values collected during the run-in period) and for each inter-visit period (i.e., [Week 0 – Week 4]; [Week 4 – Week 8] and [Week 8 – Week 12]). Missing data will be imputed as detailed in section 7.3.

Off-treatment data will be included in the analysis and a procedure based on multiple imputation techniques will be performed as described in section 7.3.1.2.2 to manage missing data due to study discontinuation. Then, an ANCOVA model overall for each inter-visit period and for the average value over 12-week treatment period will be performed as described in section 7.4. In case of issues occurring during the imputation of missing data, missing data due to study discontinuation will be imputed using a CR approach, as described in section 7.3.1.2.3.

From the model, the adjusted means in each group and the difference in adjusted means for the group comparisons will be estimated together with their 95% CIs and p-values (see section 14.1 for SAS code).

Results will be graphically summarized as follows:

- A figure with adjusted mean change (mean ± 95% CI) from baseline to each inter-visit period by treatment group derived from the ANCOVA model.

Additionally, average morning PEF at each inter-visit period and over the entire period (actual value and change from baseline) will be summarized by treatment group using descriptive statistics. This descriptive summary will not include imputed data but will include off-treatment data.

9.2.2.6 Change from Baseline in Average Evening PEF Over 12-week Treatment Period

The change from baseline in average evening PEF over 12-week treatment period will be calculated as described in section 7.8.1.

The evening PEF will be collected by the participant on a daily basis.

Variable	Derivation for descriptive analysis	Derivation for inferential analysis
Pre-dose evening best PEF	The **pre-dose evening best PEF** is defined as the highest evening PEF among the available evening PEF measurements of that day excluding those listed in section 7.11.1.	See definition on the left side.
Average pre-dose evening PEF at each inter-visit period	The **average pre-dose evening PEF at each inter-visit period** is defined as the arithmetic mean of all available pre-dose evening best PEF values recorded in each inter-visit period. Availability of at least 7 valid evening sessions per each inter-visit period are required to make the inter-visit period evaluable, otherwise the average evening PEF for that inter-visit period will be set to missing. The **inter-visit period** is defined as the time interval from the evening session of clinic visit day to the evening session of the day before the next clinic visit (or the date of end of efficacy assessment period/ discontinuation for last inter-visit period). For the first inter-visit period, the date of start of randomized treatment period will be considered as reference point instead of date of Visit 2.	See definition on the left side. Missing average-pre dose evening PEF at inter-visit period will be imputed for each subject discontinuing from the study, according to the strategy defined in section 7.3.1.2, in order to obtain one observed/imputed average-pre dose evening PEF per each of the three inter-visit periods (i.e., [Week 0– Week 4]; [Week 4 – Week 8] and [Week 8 – Week 12]). For the purpose of missing data imputation using off-treatment data, an inter-visit period will be considered: • "on-treatment" if 50% or more of the available pre-dose evening best PEF assessments of the inter-visit period are "on-treatment" assessments; • "off-treatment" if less than 50% of the available pre-dose evening best PEF assessments of the inter-visit period are "on-treatment" assessments.
Average pre-dose evening PEF over entire treatment period	The **average pre-dose evening PEF over entire treatment period** is defined as the arithmetic mean of all available pre-dose evening best PEF values recorded all over the entire treatment period. Availability of at least 1 evaluable inter-visit period is required over all treatment period to make the entire treatment period evaluable, otherwise the average evening PEF over entire treatment period will be set to missing. The **entire treatment period** is defined as the time interval from the	The **average pre-dose evening PEF over entire treatment period** is defined as the arithmetic mean of the three observed/imputed averages pre-dose evening PEF at inter-visit periods.

Variable	Derivation for descriptive analysis	Derivation for inferential analysis
	evening session of the date of start of randomized treatment period to the evening session of the date before the end of efficacy assessment period/ discontinuation.	

The analysis will be performed as described for average pre-dose morning PEF (see section 9.2.2.5), and corresponding summaries will be presented.

9.2.2.7 Proportions of Pre-dose Morning FEV_1 Responders at Week 4, 8 and 12

The pre-dose morning FEV_1 response criteria are defined as:

- Pre-dose morning FEV_1 responder: *subject who achieves a change from baseline on pre-dose morning FEV_1 ≥100 mL;*
- Pre-dose morning FEV_1 non-responder: *Otherwise*

Pre-dose morning FEV_1 response will be assessed at Visit 2 (week 0), Visit 3 (week 4), Visit 4 (week 8), Visit 5 (week 12). The change from baseline will be calculated as described in section 7.8.1. Missing data will be imputed as detailed in section 7.3.

Off-treatment data will be included in the analysis and a procedure based on multiple imputation techniques will be performed as described in section 7.3.1.3.1 to manage missing data due to study discontinuation. Then, a logistic regression model including covariates as described in section 7.4 will be performed at each visit. In case of issues occurring during the imputation of missing data, missing data due to study discontinuation will be imputed using a CR approach, as described in section 7.3.1.3.2.

From the model, the adjusted OR for the association between treatment and the response will be estimated together with 95% Cis and p-values (see Section 14.2 for SAS code).

Results will be graphically summarized as follows:

- A figure with adjusted OR (OR ± 95%CI) to each study visit derived from the logistic regression.

Additionally, pre-dose morning FEV_1 responders at Week 4, Week 8 and Week 12 visit (i.e., a subject is responder if change from baseline ≥ 100 mL) will be summarized by treatment group using descriptive statistics. This descriptive summary will not include imputed data but will include off-treatment data.

9.2.2.8 Proportions of Trough FEV_1 Responders at Week 12

The trough FEV_1 response criteria are defined as:

- Trough FEV_1 responder: *subject who achieves a change from baseline on trough FEV_1 ≥100 mL;*
- Trough FEV_1 non-responder: *Otherwise*

Trough FEV_1 response will be assessed at Visit 2 (week 0) and Visit 5 (week 12). The change from baseline will be calculated as described in section 7.8.1. Missing data will be imputed as detailed in section 7.3.

The analysis will be performed as described for pre-dose morning FEV_1 response (see section 9.2.2.8), and corresponding summaries will be presented.

9.2.2.9 Change from Baseline in Terms of ACQ-7 and ACQ-5 at Week 12.

The change from baseline in ACQ-7 and ACQ-5 at Week 12 will be calculated as described in section 7.8.1.

The Asthma Control Questionnaire (ACQ-7) is a questionnaire composed by 7 items (scores range between 0 – no impairment to 6 – maximum impairment).
The ACQ-7 score is automatically calculated on the electronical device as the arithmetic mean of all the items (only if all the 7 answers are available, otherwise the ACQ-7 is set to missing):
The ACQ-5 Score is automatically calculated on the electronical device as the arithmetic mean of the items #1 to #5 (only if all the 5 answers are available, otherwise the ACQ-5 is set to missing).

Change from baseline in ACQ-7 and ACQ-5 will be assessed at baseline (week 0), Visit 3 (week 4), Visit 4 (week 8), Visit 5 (week 12). Missing data will be imputed as detailed in section 7.3.

The analysis will be performed as described for the primary efficacy variable (see section 9.2.1.1.1), and corresponding summaries will be presented.

9.2.2.10 Change from Baseline in Percentage of Rescue Medication-free Days Over 12-week Treatment Period

The change from baseline in percentage of rescue medication free days over 12-week treatment period will be calculated as described in section 7.8.1.

The rescue medication will be collected by the participant on a daily basis.

Variable	Derivation for descriptive analysis	Derivation for inferential analysis
Rescue medication free day	A **rescue medication-free day** is a day with daily use of rescue medication = 0. For each day, the rescue medication free-day will be calculated only if data of day-time intake (recorded at evening session) and night-time intake (recorded at morning sessions of the subsequent day) are available.	See definition on the left side.

Variable	Derivation for descriptive analysis	Derivation for inferential analysis
Percentage of rescue medication-free days at each inter-visit period	The **percentage of rescue medication-free days at each inter-visit period** is defined as: (number of days with no rescue medication during the inter-visit period / number of days on which daily rescue medication use is assessed during the inter-visit period)*100. Availability of at least 7 valid days per each inter-visit period is required to make the inter-visit period evaluable, otherwise the percentage of rescue medication-free days for that inter-visit period will be set to missing. The **inter-visit period** is defined as the time interval from the evening session of the day of clinic visit to the morning session of the day of next clinic visit (or date of end of efficacy assessment period/ discontinuation for last inter-visit period).	See definition on the left side. Missing percentage of rescue medication free-days at inter-visit period will be imputed for each subject discontinuing from the study, according to the strategy defined in section 7.3.1.2, in order to obtain one observed/imputed percentage of rescue medication free-days per each of the three inter-visit periods (i.e., [Week 0– Week 4]; [Week 4 – Week 8] and [Week 8 – Week 12]). For the purpose of missing data imputation using off-treatment data, an inter-visit period will be considered: • "on-treatment" if 50% or more of the days with available assessment of the inter-visit period are "on-treatment" days; • "off-treatment" if less than 50% of the days with available assessment of the inter-visit period are "on-treatment" days.
Percentage of rescue medication-free days over entire treatment period	The **percentage of rescue medication free days over entire treatment period** is defined as (number of days with no rescue medication over entire treatment period / number of days on which daily rescue medication use is assessed over entire treatment period)*100. Availability of at least 1 evaluable inter-visit period is required over all treatment period to make the entire treatment period evaluable, otherwise the percentage of rescue medication-free days over entire treatment period will be set to missing. The **entire treatment period** is defined as the time interval from the evening session of the date of start of randomized treatment period to the morning session of the date of end of efficacy assessment period/ discontinuation.	The **percentage of rescue medication-free days over entire treatment period** is defined as the arithmetic mean of the three observed/imputed percentages of rescue medication-free days at inter-visit periods.

The analysis will be performed as described for average pre-dose morning PEF (see section 9.2.2.5), and corresponding summaries will be presented.

9.2.2.11 Change from Baseline in Percentage of Asthma Symptom-free Days Over 12-week Treatment Period

The change from baseline in percentage of asthma symptom free days over 12-week treatment period will be calculated as described in section 7.8.1.

The asthma symptom will be collected by the participant on a daily basis.

Variable	Derivation for descriptive analysis	Derivation for inferential analysis
Asthma symptom free day	An **asthma symptom-free day** is a day with total daily asthma symptom score = 0. For each day, the asthma symptom free-day will be calculated only if data of day-time symptoms (recorded at evening session) and night-time symptoms (recorded at morning sessions of the subsequent day) are available.	See definition on the left side.
Percentage of asthma symptom-free days at each inter-visit period	The **percentage of asthma symptom free days at each inter-visit period** is defined as (number of days with no asthma symptom during the inter-visit period / number of days with available daily record of asthma symptom during the inter-visit period)*100. Availability of at least 7 valid days per each inter-visit period is required to make the inter-visit period evaluable, otherwise the percentage of asthma symptom-free days for that inter-visit period will be set to missing. The **inter-visit period** is defined as the time interval from the evening session of the day of clinic visit to the morning session of the day of next clinic visit (or date of end of efficacy assessment period/ discontinuation for last inter-visit period).	See definition on the left side. Missing percentage of asthma symptom-free days at inter-visit period will be imputed for each subject discontinuing from the study, according to the strategy defined in section 7.3.1.2, in order to obtain one observed/imputed percentage of asthma symptom-free days per each of the three inter-visit periods (i.e., [Week 0– Week 4]; [Week 4 – Week 8] and [Week 8 – Week 12]). For the purpose of missing data imputation using off-treatment data, an inter-visit period will be considered: • "on-treatment" if 50% or more of the days with available assessment of the inter-visit period are "on-treatment" days; • "off-treatment" if less than 50% of the days with available assessment of the inter-visit period are "on-treatment" days.
Percentage of asthma symptom-free days over entire treatment period	The **percentage of asthma symptom-free days over entire treatment period** is defined as (number of days with no asthma symptom over entire treatment period / number of days with available daily record of asthma symptom over entire treatment period)*100. Availability of at least 1 evaluable inter-visit period is required over all treatment	The **percentage of asthma symptom-free days over entire treatment period** is defined as the arithmetic mean of the three observed/imputed percentages of asthma symptom-free days at inter-visit periods.

Variable	Derivation for descriptive analysis	Derivation for inferential analysis
	period to make the entire treatment period evaluable, otherwise the percentage of asthma symptom-free days over entire treatment period will be set to missing. The **entire treatment period** is defined as the time interval from the evening session of the date of start of randomized treatment period to the morning session of the date of end of efficacy assessment period/ discontinuation.	

The analysis will be performed as described for average pre-dose morning PEF (see section 9.2.2.5), and corresponding summaries will be presented.

10 Safety Analyses

All analyses of safety variables will be performed on the Safety set. For subjects who discontinue the randomized study drug but remain in the study, assessments conducted following 1 week after the last dose of study drug will not be considered in the analysis or presentation of safety data.

10.1 Extent of Exposure

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

- Date of last randomized study medication intake – date of first randomized study medication intake + 1.

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

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

Descriptive statistics of extent of exposure (weeks) will be provided by treatment group.
The number and the percentage of subjects with the following 4-week categories of extent of exposure will also be presented:

- [0-4) weeks.
- [4-8) weeks.
- [8, 12 (weeks-ETD)].

10.2 Adverse Events

10.2.1 Definitions

AEs summaries will include adverse events and asthma exacerbations CRF pages.

The AEs will be classified according to the following rules:

- Pre-treatment AE: Any adverse events started after the informed consent signature and before the first study drug intake will be classified as pre-treatment adverse events:

  - date of informed consent < AE onset date < date of first randomized study medication intake.
- Treatment emergent AE (TEAE): All adverse events starting on or after the first study drug intake and up to 1 week after the last dose of study drug intake will be classified as treatment emergent adverse even (TEAE):
  - date of first randomized study medication intake ≤ AE onset date ≤ date of last randomized study medication intake + 7 days.
- Post-treatment AE: Any adverse events started later than 1 week after the last dose of study drug will be considered as post-treatment adverse events.
  - AE onset date > date of last randomized study medication intake + 7 days.

The AEs will also be classified in the following categories:

- A SAE is an AE judged as serious.
- An ADR is an AE judged as related to the study medication.
- A serious ADR is a SAE judged as related to the study medication.
- A severe AE is an AE with severe intensity.
- An AE leading to study drug discontinuation is an AE with action taken with study drug equal to "Drug permanently withdrawn".
- An AE leading to death is an AE with outcome equal to "Fatal".

If severity or relationship is found to be missing, the worst severity category (severe > moderate > mild) and/or strongest study drug relationship category (related > not related) will be imputed.

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

- For pre-treatment AEs:
  - AE onset date – date of first randomized study medication intake (if AE onset date is completely known);
  - missing (if AE onset date is incomplete or unknown).
- For TEAEs:
  - AE onset date – date of first randomized study medication intake +1 (if AE onset date is completely known);
  - missing (if AE onset date is incomplete or unknown).

The duration of an AE will be calculated as follows:

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

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

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

10.2.2 Descriptive Analysis

Pre-treatment AEs, TEAEs and post-treatment AEs will be presented separately.

Pre-treatment AEs and post-treatment AEs will be presented in the listings only.

TEAEs, drug related TEAEs (i.e., ADRs), serious TEAEs, non-serious TEAEs, serious ADRs, TEAEs leading to study drug discontinuation and TEAEs leading to death will be summarized by treatment arm. Summaries will be presented overall (number and percentage of subjects having at least one event, total number of events and incidence density) and by System Organ Class (SOC) and by Preferred Term (PT) sorted by alphabetical order.

The incidence density will be estimated by number of subjects with at least one event divided by the total person-years of exposure to study drug, i.e.

(Number of subject with at least one event / total person-years) * 100

The denominator will be the total person-years, which is the sum of person-years of all subjects of their respective exposure period (in person-years) calculated as

(Last dose date – first dose date +8) / 365.25

For each of the summaries done at the participant level, multiple occurrences of the same event within a participant will be counted once in the summaries by SOC and PT; multiple occurrences of the same event within a participant will be counted once in the worst severity category (severe > moderate > mild) and/or strongest study drug relationship category (related > not related).

The number of subjects who are diagnosed for COVID-19 will be also summarized in the Safety Set.

Analysis of TEAEs comparing Treatment Groups

Comparative analysis of treatment emergent adverse events will be performed as follow:.

- The number of subjects who experienced at least one treatment emergent AE, SAE, ADR, serious ADR, severe AE, AE leading to discontinuation, AEs leading to death will be also compared between treatment groups in terms of risk difference. The risk difference will be calculated considering the crude proportion of subjects with the selected event in the two treatment groups (i.e., number of subjects of the treatment group with the selected event / number of subjects of the treatment group). The 95% CI for the risk difference will be calculated using the Newcombe Hybrid Score method [10] (see section 14.4 for SAS code).
- The number of subjects who experienced at least one treatment emergent AE by SOC, AE by PT, SAE by SOC, SAE by PT will be compared between treatment groups with the same methodology described above in the previous bullet point.

For the analysis comparing treatment groups described in the bullet points above, adverse events data will be also visualized with outputs including two-panels display with:

1. Plotted proportions and
2. Forest plot with risk differences (95% CI).

Note: For the analyses comparing treatment groups described in the bullet points above, the comparative analysis (i.e., estimation of risk difference and its 95% CI) will not be carried out if the total number of subjects with the event in the overall Safety Set is < 5.

Descriptive Analysis of Class-related Adverse Events

Class-related Adverse Events will be grouped into the following medical concepts according to the TEAE SOC and PT. The final categorization of TEAEs into medical concepts will be defined by the study team during the blinded review of the data and finalized before the database lock.

Class related Adverse Events	
Medical concept 1	**Medical concept 2**
ICS class related AEs	Lower Respiratory Tract Infections (including pneumonia)
	Candidiasis
	Ocular effects
	Decreased bone density
	Adrenal suppression
	Local steroid effects
LABA class related AEs	Cardiovascular effects
	Effects on glucose
	Effects on potassium
	Muscle spasms
	Tremor

Summaries of class related TEAEs will be presented will be presented overall and by medical concepts.

Pre-treatment AEs, TEAEs and post-treatment AEs will be presented separately. Pre-treatment AEs and post-treatment AEs will be presented in the listings only. At least one TEAE, at least one drug related TEAE (i.e., ADR), at least one serious TEAE, at least one non-serious TEAE, at least one serious ADRs, at least one TEAE leading to study drug discontinuation, at least one TEAE leading to death will be summarized by treatment arm. Summaries will be presented overall (number and percentage of subjects having at least one event, total number of events and incidence density [i.e., number of subjects with at least one event divided by the total person-years of exposure to study drug]) and by medical concepts.

Comparative analysis of class-related TEAEs comparing treatment groups will be performed in the safety set using on-treatment data only.

- The number of subjects who experienced at least one treatment emergent AE, SAE, ADR, serious ADR, severe AE, AE leading to discontinuation, AEs leading to death will be also compared between treatment groups in terms of risk difference. The risk difference will be calculated considering the crude proportion of subjects with the selected event in the two treatment groups (i.e., number of subjects of the treatment group with the selected event / number of subjects of the treatment group). The 95%

Cis for the risk difference will be calculated using the Newcombe Hybrid Score method [10].

- The number of subjects who experienced at least one treatment emergent AE by medical concept 1, AE by medical concept 2, SAE by medical concept 1, SAE by medical concept 2 will be compared between treatment groups with the same methodology described in the previous bullet point.

For the analysis comparing treatment groups described in the bullet points above, adverse events data will be also visualized with outputs including two-panels display with:

1. plotted proportions and
2. forest plot with risk differences (95% CI).

10.3 Vital Signs and Body Weight

Vital signs (systolic and diastolic blood pressure and pulse rate) and body weight along with changes from baseline will be summarized by treatment group in the Safety Set using on-treatment data only with descriptive statistics and the 95% CI of the mean.

10.4 ECG

Pre-dose 12-lead ECG parameters (HR, QTcF, QRS and PR) and their changes from baseline as well as the changes from pre-dose to 30 minutes, 1, 4 and 12 hours post-dose of the same day at each scheduled post-baseline study visit will be summarized by treatment in the Safety Set using on-treatment data only with descriptive statistics and the CI of the mean (95% CI for absolute values and 90% CI for the changes from baseline).

The number and the percentage of subjects with a:

- QTcF >450 ms, >480 ms and >500 ms for males and QTcF >470 ms and >500 ms for females.
- Change from baseline to pre-dose of each post-treatment visit in QTcF in the intervals >30 ms and >60 ms.
- Change from pre-dose to 30 minutes, 1, 4 and 12 hours post-dose of the same day in QTcF in the intervals >30 ms and >60 ms

At each post-baseline visit and at any post-baseline visit (also including the unscheduled visits) will be also presented by treatment group in the Safety Set.

Pre-dose and 30 minutes, 1, 4 and 12 hours post-dose ECG interpretation from investigator at each scheduled visit will be summarized using number and percentage by treatment group in the Safety Set using on-treatment data only.

10.5 Laboratory Data

The following parameters will be assessed by a central laboratory:

- Hematology: red blood cells count (RBC), white blood cells count (WBC), and differential (neutrophils, basophils, eosinophils, lymphocytes, monocytes – absolute and %), total hemoglobin (Hb), hematocrit (Hct), platelets count (PLT).
- Serum chemistry: fasting glucose, blood urea nitrogen (BUN) or urea, cholesterol, triglycerides, creatinine, creatinine phosphokinase (CPK)uric acid, aspartate

aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), total bilirubin, bilirubin direct and indirect, alkaline phosphatases, albumin, total proteins, sodium, potassium, calcium, and chloride electrolytes, phosphate.

Actual values and change from baseline will be summarized by treatment using descriptive statistics and 95% CI of the mean at each scheduled visit in the Safety Set using on-treatment data only.
Shift tables from screening/baseline to Week 12, with regard to normal range (low CS, low NCS, normal, high NCS, high CS), will be presented by treatment group for each laboratory parameter.

All laboratory data will be listed with abnormal values flagged.

Results of the serum pregnancy and urine pregnancy tests will only be listed.

10.6 Physical Examination

Physical examinations data collected during the study will only be listed.

11 Other Analyses

11.1 Oropharyngeal Examination

Oropharyngeal examinations data collected during the study will only be listed.

12 Changes in the Planned Analyses from Study Protocol

- The protocol in Section 12.3.4, in main estimand paragraph stated for the missing imputation technique:

Note: In case of collection of very few off-treatment data such that the planned imputation cannot be performed, the imputation of missing data after study discontinuation will be based on the Copy Reference (CR) approach (i.e. considering the data distribution of the CHF 718 pMDI 800µg TDD arm, including both on-treatment and off-treatment data) for both treatment arms.

In the SAP section 7.3.1 has been set the limit of off-treatment data. The planned imputation technique will be applied if at least 5% of the analyzed population (ITT) consented to continue the study after treatment discontinuation and attended visit 5 off-treatment.

- In Section 10.2.2, the definition of medical concepts for ICS class-related adverse events was updated, compared with the definition reported in the study protocol at Section 12.3.7 due to a review from Pharmacovigilance unit post-DRM, with the addition of the "Local Steroid Effect" category.

13 Output

13.1 Software

SAS version 9.4 will be used to perform all the statistical analyses.

13.2 Reporting Conventions

13.2.1 Treatment, Visit and Subgroup Descriptors

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

Treatment (as displayed in outputs)	Descriptor for treatment
Run-In Period	**CHF 718 pMDI 100µg** Beclomethasone dipropionate (BDP) 100µg use only in run-in period. Dose regimen: BDP 100µg per actuation, 2 or 4 inhalations (puffs) BID, total daily dose (TDD) 400µg or 800µg.
CHF 1535	**CHF 1535 pMDI 800/24µg TDD** and Placebo Fixed combination of extrafine BDP 200µg plus FF 6µg (BDP/FF). Dose regimen: BDP/FF 200/6µg per actuation, 2 inhalations (puffs) BID, total daily dose (TDD) 800/24µg + 2 inhalations (puffs) BID of Placebo.
CHF 718	**CHF 718 pMDI 100µg TDD** Beclomethasone dipropionate (BDP) 100µg. Dose regimen: BDP 100µg per actuation, 4 inhalations (puffs) BID, total daily dose (TDD) 800µg.

Output	Descriptor for visits
Tables	**Visits:** Visit 0 (Week -3), Visit 1 (Week -2), Visit 2 (Week 0, Day 1), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12) and Visit 6 (Week 13 – FU). **Inter-visit Period:** V1-V2 (W-2-W0), V2-V3 (W0-W4), V3-V4 (W4-W8), V4-V5 (W8-W12), V5-V6 (W12-W13).
Listings	**Visits:** Just the visit number (0, 1, 2, 3, 4, 5…) or "ETD", "FU", "Unscheduled x.xx" will be presented in the "Visit" column. **Inter-visit Period:** V1-V2 (W-2-W0), V2-V3 (W0-W4), V3-V4 (W4-W8), V4-V5 (W8-W12), V5-V6 (W12-W13).
Figures	**Visits:** V0, V1, V2, V3, …, V6 Note: if the space between visit is relevant, week number (-2, 0, 4, 8, 12, 13) should be used and the scale respected. Weeks should appear in the label.

Subgroup	Category descriptor
Age	• <65, • ≥65
Sex	• Male • Female
BMI	• <25 • 25-<30 • ≥30
Smoking Status	• Non-smoker • Ex-smoker
Pre-bronchodilator FEV_1	• Mild: >65% • Moderate:50%-65% • Severe: <50%
Race	• White • Black or African American • Other (Other; American Indian or Alaska Native; Asian; Native Hawaiian or Other Pacific Islander)
Race & Ethnicity Combined	• White/Non-Hispanic • Black/Non-Hispanic • Hispanic

* Final decision to be taken before Database Lock, see section 7.6.

13.2.2 Decimal Places

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

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

Variables	Decimal Places
• Duration of AE, medication (days) • Duration of treatment of asthma exacerbations with systemic corticosteroids, and hospitalization for asthma exacerbations (days) • Treatment exposure (days) • Number of pack-years • Morning PEF • Evening PEF	0 decimal

Variables	Decimal Places
• Duration of smoking (years) • BMI (kg/m2) • Time since first asthma diagnosis (months) • Time since last documented asthma exacerbation (months) • Time to study discontinuation (weeks) • Time to treatment discontinuation (weeks) • Compliance (%) to study medication and to diary use • Percentage of days without intake of rescue medication (%) • ACQ-5 Score, ACQ-7 Score (Total and per Domains) • AE incidence density	1 decimal
• Follow-up time (years) • Average use of rescue medication • Total Daily asthma symptoms score	2 decimals
• 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):

Statistic	Number of decimal places for reporting
Counts (n)	None
Percentages (%)/Proportion	1 decimal place *Note:* *If the calculated percentage is >0.0% but <0.1% then <0.1% is to be presented in the relevant table and/or listing.* *If the calculated percentage is >99.9% but <100.0% then >99.9% is to be presented in the relevant table and/or listing.*
Mean, Median, SD, 25th percentile, 75th percentile, Confidence intervals	Actual data + 1 decimal place
Kaplan-Meier survival probabilities	3 decimal places
Asthma Exacerbation rate, adjusted rate ratio and its confidence limits	3 decimal places
P-values	In general, 3 decimal places *Note:* *If the p-value is less than 0.001, it will be presented as <0.001.* *If the p-value is greater than 0.999, it will be presented as >0.999.*

Statistic	Number of decimal places for reporting
Difference between percentages (%)/ Proportions and confidence limits	Actual data + 1 decimal place
Odds ratio estimates and confidence limits	3 decimal places
Min, Max	Same as actual data

All summary statistics will be rounded (using the SAS® function ROUND) and wherever possible data will be decimal aligned.

13.2.3 Other Reporting Conventions

Treatment will be presented in the tables with the following order: CHF 1535 (Test Treatment A), CHF 718 (Reference Treatment B).

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

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

All tables will have their source listing referenced in a footnote. All figures will include the source table in a footnote. Listings should be sorted as explained in section 7.12 and have the SDTM and/or ADaM source data referenced in a footnote. The columns of each listing should fit into one page and should not be split into different pages.

When an output is split in multiple pages, page-break should be adequately controlled.

When a table is split in multiple pages, breaking of a block information in different pages is not allowed.

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number and any other relevant information which is split between 2 pages) must be presented at the beginning of that page.

When a listing contains a lot of information, in order to optimize space on the page, some columns can be merged (e.g., "reported term" and "indication" may be presented in the same column.

13.3 Format

The following information should always be presented:

- 'Clinical Study Code No.:<Study Code No.>' followed by Chiesi denomination in the top portion of each page. Chiesi denomination is 'Chiesi Farmaceutici S.p.A'.
- The table/listing/figure number followed by the title, the analysis set used and the output page number in the format of 'Page x of Y' in the top portion of each page of any table/listing/figure.
- The SAS program name followed by the datetime of the output production and the analysis type (e.g., Dry Run; Draft Version; Final Version) in the bottom portion of each page of any table/listing/figure. The source listing/table/dataset will appear bottom left for every table/figure/listing.
- Tables and listings will be produced in rich text format (i.e., they will be tabular in format). Individual outputs must be provided in both portable format document (.pdf) and rich text format (.rtf).
- Combined PDF and RTF documents must also be provided, including a table of contents with hyperlinks. The combined documents should be divided by document type (tables, figures, listings).
- SAS outputs will be provided to the Sponsor in a similar manner (PDF and RTF; combined and with hyperlinked table of contents). The SAS outputs will be a separate deliverable to the Sponsor and are not intended for inclusion within the CSR.
- The combined documents page number in the format of 'Page n of N' will be presented bottom right corner.

The following should be followed for the tables:

- A landscape layout and Letter size will be used.
- A 9-point font size will be used using Courier New font.
- Horizontal lines will appear before and after the column heading of the output.
- Additional footnotes may be included if strictly necessary for clarification. Footnotes will be put under the main body of text at the bottom left of the page and will be displayed on each page of the output and not only on the last one.
- The left and right margins will be a minimum of 2.1 cm from the left and 1.9 cm from the right. The top and bottom margins will be a minimum 2.92 cm. Header and footer will be both 1.27 cm.

The following should be followed for the listings:

- A landscape layout and Letter size will be used.
- An 8-point font size will be used using Courier New font.
- Horizontal lines will appear before and after the column heading of the output.
- Additional footnotes may be included if strictly necessary for clarification. Footnotes will be put under the main body of text at the bottom left of the page and will be displayed on each page of the output and not only on the last one.
- The left and right margins will be a minimum of 2.1 cm from the left and 1.9 cm from the right. The top and bottom margins will be a minimum 2.92 cm. Header and footer will be both 1.27 cm.

The following should be followed for the figures:

- A portrait layout and Letter size will be used.
- A 9-point font size will be used using Courier New font.
- Figures will be produced in RTF and PDF formats (as described above), including relevant titles and footnotes as separate elements on the page (not within the body of the figure).
- Additional footnotes may be included if strictly necessary for clarification. Footnotes will be put under the main body of text at the bottom left of the page and will be displayed on each page of the output and not only on the last one.
- The size of the figures will be: width=16.3 cm height=12.2 cm. The resolution will be set using the option IMAGE_DPI=400. Figures will have a footer specifying the source table or listing. Figures should clearly identify each treatment and require care of colors/symbols.

The left margin will be a minimum of 2.5 cm, the right margin will be a minimum of 2 cm. The top and bottom margins will be a minimum 0.8 cm.

13.4 Quality Control

The Quality Control steps will be defined in the Datasets, Tables, Listings, Figures QC Plan.

The following steps will be taken to ensure the quality of the outputs:

- The author of each table/listing/figure program will review the program and will verify that no error message is highlighted in the 'LOG' file.
- Tables and figures will be independently programmed form the raw datasets by a second statistician/programmer and outputs will be compared either electronically (by comparing the data being tabulated using PROC COMPARE) or by manually comparing the data in the two independent outputs.
- Listings will be checked either electronically (by comparing the data being listed using PROC COMPARE) or by manually comparing the data in the listings to the raw/derived data.
- All outputs will be compared to the shells.
- Related outputs will be compared for consistency.

14 SAS Code

The SAS codes should be only considered as guidance and may be slightly modified in the actual SAS code based on the datasets structure and outputs display.

14.1 ANCOVA Model

```
PROC MIXED DATA = dataset;
    CLASS tmt region priortmt;
    MODEL change = tmt region priortmt baseline;
```

LSMEANS tmt / OM CL;
LSMESTIMATE tmt "CHF 1535 vs CHF 718" 1 -1 / CL;
RUN;

***Notes**:*

- Change (numeric) represents the change from baseline (i.e., value at visit – baseline value) to each visit of the variable;
- Tmt (character – 2 levels, "CHF 1535" vs. "CHF 718") represents the randomized treatment group;
- Priortmt (character – 3 levels, "High dose ICS" vs. "Medium dose ICS" vs. "Medium dose ICS/LABA") represents the prior asthma therapy;
- Region (character – 4 levels, "Northeast" vs. "Midwest" vs. "South" vs. "West") represents the US region;
- Baseline (numeric) represents the baseline value of the variable;

14.2 Logistic Regression Model

PROC GENMOD DATA = dataset;
CLASS response(REF="N") tmt region priortmt;
MODEL Response = tmt region priortmt baseline / DIST=BINOMIAL WALD TYPE3;
*LSMESTIMATE tmt "*CHF 1535 *vs* CHF 718*" 1-1/EXP CL;*
RUN;

Notes:

- Response (character – 2 levels, "Y" vs. "N") represents the binary variable for each subject;
- Tmt (character – 2 levels, "CHF 1535" vs. "CHF 718") represents the randomized treatment group;
- Priortmt (character – 3 levels, "High dose ICS" vs. "Medium dose ICS" vs. "Medium dose ICS/LABA") represents the prior asthma therapy;
- Region (character – 4 levels, "Northeast" vs. "Midwest" vs. "South" vs. "West") represents the US region;
- Baseline (numeric) represents the baseline value of the corresponding parameter.

14.3 Kaplan Meier Estimate and Log-Rank Test

PROC LIFETEST DATA=dataset TIMELIST = (list_of_times) OUTSURV=stim REDUCEOUT PLOTS=survival(TEST ATRISK);
*TIME time*censor (1);*
STRATA tmt;
RUN;

Notes:

- Time (numeric) represents the time to event or time to censoring;
- Censor (numeric) represents the censoring indicator (1 = censored);
- Tmt (character – 2 levels, "CHF 1535" vs. "CHF 718") represents the randomized treatment group;
- For the time to treatment discontinuation, the *list_of_times* is (3.9999999, 7. 9999999, EOT), where EOT should be replaced by the last time to treatment discontinuation.

- For the time to discontinuation from the study, the *list_of_times* is (3.9999999, 7. 9999999, 11.999999, EOS), where EOS should be replaced by the last time to study discontinuation >12 weeks (if any).

14.4 Risks Differences

```
PROC FREQ DATA=dataset;
        TABLES tmt*var / RISKDIFF (COLUMN=2 CL=(NEWCOMBE));
        WEIGHT count;
RUN;
```

Notes:

- Tmt (character – 2 levels, "CHF 1535" vs. "CHF 718") represents the actual treatment group;
- Var (categorical – 2 levels, "Y" vs. "N") represents the binary flag for the occurrence of one of the variables of interest: TEAE, SOC or PT;
- Count (numeric) represent the count of distinct subjects with a least one occurrence or no occurrence at all of the variable of interest.

14.5 Imputation of Intermittent Missing Data

As preliminary note, *dataset* should contain one row per each subject, with the values of selected parameter collected at each study visit (i.e., *V2, V3, V4* and *V5*) reported as different columns.

```
/* Imputation of intermittent missing data if intermittent missing data is present in the raw
data */
PROC MI DATA=dataset SEED=14823 NIMPUTE=1000 OUT=monotone NOPRINT;
        VAR trt01pn region_dummy1-region_dummy3 priortmt_dummy1 priortmt_dummy2
        baseline v2 v3 v4 v5;
        MCMC CHAIN=MULTIPLE IMPUTE=MONOTONE NBITER=1000 NITER =500;
RUN;
```

Notes:

- *Trt01pn* (numeric – 2 levels) represents the planned treatment group. No need to create dummy variables since it is a dichotomous variable (i.e., with only two levels as data);
- *Region* (numeric – 4 levels) represents the stratification factor for US region. Need the creation of 3 dummy variables (*region_dummy1-region_dummy3*). *region_dummy1*=1 if *region*="Northeast", 0 otherwise. *Region_dummy2*=1 if *region*="Midwest", 0 otherwise. *Region_dummy3*=1 if *region*="South", 0 otherwise;
- *Priortmt* (numeric – 3 levels) represents the stratification factor for prior asthma therapy. Need the creation of 2 dummy variables (*priortmt_dummy1 priortmt_dummy2*).
  priortmt_dummy1=1 if *priortmt*="Medium dose ICS/LABA", 0 otherwise. *Priortmt_dummy2*=1 if *priortmt*="Medium dose ICS", 0 otherwise;
- *Baseline* (numeric) represents the baseline value of the corresponding parameter;
- *v2, v3, v4* and *v5* (numeric) represent the values of the corresponding parameter collected at each study visit.

14.6 Imputation of Monotone Missing Data Using Available Off-treatment Data

As preliminary note, this is just an example which will need to be adapted considering the relevant visit / inter-visit periods for the analyzed endpoint and *dataset* should contain:

- one row per each subject;
- the values of selected efficacy parameter collected at each post-baseline visit (i.e., *V2, V3, V4* and *V5*) reported as different columns;
- for each planned post-baseline assessment, an indicator variable (i.e., *ONTRT2, ONTRT3, ONTRT4, ONTRT5*) in order to identify if the assessment is on-treatment (i.e., *ONTRT2-ONTRT5* = 1) or off-treatment (i.e., *ONTRT2-ONTRT5* = 0). These indicator variables will be always populated, regardless of whether the assessment is collected or not;
- Treatment (i.e., 1="CHF 1535" and 2="CHF 718") and other relevant covariates.

Below an example of the structure of the starting dataset.

USUBJID	TRT01PN	V2	V3	V4	V5	ONTRT2	ONTRT3	ONTRT4	ONTRT5
1	1	CON	CON	CON	COFF	1	1	1	0
2	2	CON	CON	CON	NCON	1	1	1	1
3	1	CON	CON	COFF	COFF	1	1	0	0

Note: CON = Value collected while on-treatment; COFF = Value collected while off-treatment; NCON = Value not collected while on-treatment; NCOFF = Value not collected while off-treatment

Step 1: Applying Monotone Pattern (step applicable only in case of intermittent missing data, otherwise step should be skipped)

See section 14.5.

Step 2: First Planned Post-Baseline Assessment (i.e., Visit 2)

2.1 Preliminary check

(if Step 1 was performed)

```
/* Checking the 'stability' of the model if intermittent missing data imputed */
PROC MIXED DATA=monotone;
        WHERE _imputation_=1;
        CLASS trt01pn region priortmt ontrt2;
        MODEL v2= trt01pn region priortmt baseline ontrt2 trt01pn*ontrt2 / SOLUTION;
        LSMEANS trt01pn / DIFFS;
RUN;
```

(if Step 1 was NOT performed)

```
/* Checking the 'stability' of the model if no-intermittent missing data */
PROC MIXED DATA=dataset;
        CLASS trt01pn region priortmt ontrt2;
        MODEL v2= trt01pn region priortmt baseline ontrt2 trt01pn*ontrt2 / SOLUTION;
        LSMEANS trt01pn / DIFFS;
RUN;
```

- Note: if one or more regression coefficients included in the MODEL statement are not estimated successfully or if the estimation of the standard error of the treatment

difference is greater than 10 times the size of the estimate of treatment difference, then this algorithm will stop and this imputation techniques will be disregarded. Missing data will then be imputed according to the Copy-Reference approach (see section 14.7).

2.2 Multiple imputation procedure for missing values at 1st planned post-baseline assessment (i.e., Visit 2)

(step applicable only in case of missing data at Visit 2; otherwise, step should be skipped)

(if Step 1 was performed)

```
/* Impute 1st planned post-baseline assessment if intermittent missing data imputed */
PROC MI DATA=monotone SEED=14823 NIMPUTE=1 OUT=v2_imputed NOPRINT;
        BY _imputation_;
        CLASS trt01pn region priortmt ontrt2;
        VAR trt01pn region priortmt baseline ontrt2 v2;
        MONOTONE REG (v2= trt01pn region priortmt baseline ontrt2 trt01pn*ontrt2 /
        DETAILS);
RUN;
```

(if Step 1 was NOT performed)

```
/* Impute 1st planned post-baseline assessment if no-intermittent missing data */
PROC MI DATA=dataset SEED=14823 NIMPUTE=1000 OUT=v2_imputed NOPRINT;
        CLASS trt01pn region priortmt ontrt2;
        VAR trt01pn region priortmt baseline ontrt2 v2;
        MONOTONE REG (v2= trt01pn region priortmt baseline ontrt2 trt01pn*ontrt2 /
        DETAILS);
RUN;
```

2.3 Estimation of residuals for Visit 2

(step to be performed in case of missing data at Visit 2)

(if Step 1 was performed)

Calculate predicted values for Visit 2

```
/* Predicted values from the model if intermittent missing data imputed */
PROC MIXED DATA=monotone;
        BY _imputation_;
        CLASS trt01pn region priortmt ontrt2;
        MODEL v2= trt01pn region priortmt baseline ontrt2 trt01pn*ontrt2 /
        OUTP=v2_pred (RENAME=(PRED=predicted2) KEEP=_imputation_ usubjid pred)
        S;
RUN;
```

Calculate residuals for Visit 2

```
/* Predicted values and Imputed values table if intermittent missing data imputed */
PROC SQL;
        CREATE TABLE v2_resid AS
        SELECT v2_imputed.*, v2_pred.predicted2
        FROM v2_imputed, v2_pred
        WHERE v2_imputed._imputation_ = v2_pred._imputation_ AND v2_imputed.usubjid
        = v2_pred.usubjid;
```

QUIT;

/ Residuals values (difference between predicted values and imputed values) if intermittent missing data imputed */*
DATA v2_resid; SET v2_resid;
resid2= v2-predicted2;
RUN;

(if Step 1 was NOT performed)
Calculate predicted values for Visit 2
/ Predicted values from the model if no-intermittent missing data */*
PROC MIXED DATA=dataset;
CLASS trt01pn region priortmt ontrt2;
*MODEL v2= trt01pn region priortmt baseline ontrt2 trt01pn*ontrt2 /*
OUTP=v2_pred (RENAME=(PRED=predicted2) KEEP=usubjid pred) S;
RUN;

Calculate residuals for Visit 2
/ Predicted values and Imputed values table if no-intermittent missing data */*
PROC SQL;
CREATE TABLE v2_resid AS
SELECT v2_imputed., v2_pred.predicted2*
FROM v2_imputed, v2_pred
WHERE v2_imputed.usubjid = v2_pred.usubjid;
QUIT;

/ Residuals values (difference between predicted values and imputed values) if no-intermittent missing data */*
DATA v2_resid; SET v2_resid;
resid2= v2-predicted2;
RUN;

(step to be performed in case of NO missing data at Visit 2, and hence Step 2.2 was skipped)
(if Step 1 was performed)
Calculate residual values for Visit 2
/ Residual values if intermittent missing data imputed and if no missing data at Visit 2*/*
PROC MIXED DATA=monotone;
BY _imputation_;
CLASS trt01pn region priortmt ontrt2;
*MODEL v2= trt01pn region priortmt baseline ontrt2 trt01pn*ontrt2 /*
OUTP=v2_resid (RENAME=(RESID=resid2) DROP=pred stderrpred df alpha lower upper) S;
RUN;

(if Step 1 was NOT performed)
Calculate residual values for Visit 2
/ Residual values if no-intermittent missing data imputed and if no missing data at Visit 2 */*

```
PROC MIXED DATA=dataset;
        CLASS trt01pn region priortmt ontrt2;
        MODEL v2= trt01pn region priortmt baseline ontrt2 trt01pn*ontrt2 /
        OUTP=v2_resid (RENAME=(RESID=resid2) DROP=pred stderrpred df alpha lower
        upper) S;
RUN;
```

Step 3: Subsequent Planned Post-Baseline Assessment (i.e., Visit 3)

3.1 Preliminary check

```
/* Checking the 'stability' of the model */
PROC MIXED DATA=v2_resid;
        WHERE _imputation_=1;
        CLASS trt01pn region priortmt ontrt3;
        MODEL v3= resid2 trt01pn region priortmt baseline ontrt3 trt01pn*ontrt3 /
        SOLUTION;
        LSMEANS trt01pn / DIFFS;
RUN;
```

- Note: if one or more regression coefficients included in the MODEL statement are not estimated successfully or if the estimation of the standard error of the treatment difference is greater than 10 times the size of the estimate of treatment difference, then this algorithm will stop and this imputation techniques will be disregarded. Missing data will then be imputed according to the Copy-Reference approach (see section 14.7).

3.2 Multiple imputation procedure for missing values at Visit 3

(step applicable only in case of missing data at Visit 3; otherwise, step should be skipped)

```
/* Impute 2nd planned post-baseline assessment (e.g., Visit 3) if missing data at Visit 3 */
PROC MI DATA=v2_resid SEED=14823 NIMPUTE=1 OUT=v3_imputed NOPRINT;
        BY _imputation_;
        CLASS trt01pn region priortmt ontrt3;
        VAR trt01pn region priortmt baseline resid2 ontrt3 v3;
        MONOTONE REG (v3= resid2 trt01pn region priortmt baseline ontrt3
        trt01pn*ontrt3 / DETAILS);
RUN;
```

3.3 Estimation of residuals for Visit 3

(step to be performed in case of missing data at Visit 3)

Calculate predicted values for Visit 3

```
/* Predicted values of the model if missing data at Visit 3 */
PROC MIXED DATA=v2_resid;
        BY _imputation_;
        CLASS trt01pn region priortmt ontrt3;
        MODEL v3= resid2 trt01pn region priortmt baseline ontrt3 trt01pn*ontrt3 /
        OUTP=v3_pred (RENAME=(PRED=predicted3) KEEP=_imputation_ usubjid pred)
        S;
RUN;
```

Calculate residuals for Visit 3

```
/* Predicted values and imputed values table if missing data at Visit 3 */
```

```
PROC SQL;
        CREATE TABLE v3_resid AS
        SELECT v3_imputed.*, v3_pred.predicted3
        FROM v3_imputed, v3_pred
        WHERE v3_imputed._imputation_ = v3_pred._imputation_ AND v3_imputed.usubjid
        = v3_pred.usubjid;
QUIT;

/* Residuals values (difference between predicted values and imputed values) if missing data
at Visit 3 */
DATA v3_resid; SET v3_resid;
        resid3= v3-predicted3;
RUN;
```

(step to be performed in case of NO missing data at Visit 3, and hence Step 3.2 was skipped)

Calculate residual values for Visit 3

```
/* Residuals values if no missing data at Visit 3 */
PROC MIXED DATA=v2_resid;
        BY _imputation_;
        CLASS trt01pn region priortmt ontrt3;
        MODEL v3= resid2 trt01pn region priortmt baseline ontrt3 trt01pn*ontrt3 /
        OUTP=v3_resid (RENAME=(RESID=resid3) DROP=pred stderrpred df alpha lower
        upper) S;
RUN;
```

Step 4: Subsequent Planned Post-Baseline Assessment (i.e., Visit 4)

4.1 Preliminary check

```
/* Checking the 'stability' of the model */
PROC MIXED DATA=v3_resid;
        WHERE _imputation_=1;
        CLASS trt01pn region priortmt ontrt4;
        MODEL v4= resid2 resid3 trt01pn region priortmt baseline ontrt4 trt01pn*ontrt4 /
        SOLUTION;
        LSMEANS trt01pn / DIFFS;
RUN;
```

- Note: if one or more regression coefficients included in the MODEL statement are not estimated successfully or if the estimation of the standard error of the treatment difference is greater than 10 times the size of the estimate of treatment difference, then this algorithm will stop and this imputation techniques will be disregarded. Missing data will then be imputed according to the Copy-Reference approach (see section 14.7).

4.2 Multiple imputation procedure for missing values at Visit 4

(step applicable only in case of missing data at Visit 4; otherwise, step should be skipped)

```
/* Impute 3rd planned post-baseline assessment (e.g., Visit 4) if missing data at Visit 4 */
PROC MI DATA=v3_resid SEED=14823 NIMPUTE=1 OUT=v4_imputed NOPRINT;
        BY _imputation_;
        CLASS trt01pn region priortmt ontrt4;
```

```
        VAR trt01pn region priortmt baseline resid2 resid3 ontrt4 v4;
        MONOTONE REG (v4= resid2 resid3 trt01pn region priortmt baseline ontrt4
        trt01pn*ontrt4 / DETAILS);
RUN;
```

4.3 Estimation of residuals for Visit 4

(step to be performed in case of missing data at Visit 4)

Calculate predicted values for Visit 4

```
/* Predicted values of the model if missing data at Visit 4 */
PROC MIXED DATA=v3_resid;
        BY _imputation_;
        CLASS trt01pn region priortmt ontrt4;
        MODEL v4= resid2 resid3 trt01pn region priortmt baseline ontrt4 trt01pn*ontrt4 /
        OUTP=v4_pred (RENAME=(PRED=predicted4) KEEP=_imputation_ usubjid pred)
        S;
RUN;
```

Calculate residuals for Visit 4

```
/* Predicted values and imputed values table if missing data at Visit 4 */
PROC SQL;
        CREATE TABLE v4_resid AS
        SELECT v4_imputed.*, v4_pred.predicted4
        FROM v4_imputed, v4_pred
        WHERE v4_imputed._imputation_ = v4_pred._imputation_ AND v4_imputed.usubjid
        = v4_pred.usubjid;
QUIT;

/* Residuals values (difference between predicted values and imputed values) if missing data
at Visit 4 */
DATA v4_resid; SET v4_resid;
        resid4= v4-predicted4;
RUN;
```

(step to be performed in case of NO missing data at Visit 4, and hence Step 4.2 was skipped)

Calculate residual values for Visit 4

```
/* Residuals values if no missing data at Visit 4 */
PROC MIXED DATA=v3_resid;
        BY _imputation;
        CLASS trt01pn region priortmt ontrt4;
        MODEL v4= resid2 resid3 trt01pn region priortmt baseline ontrt4 trt01pn*ontrt4 /
        OUTP=v4_resid (RENAME=(RESID=resid4) DROP=pred stderrpred df alpha lower
        upper) S;
RUN;
```

Step 5: Last Planned Post-Baseline Assessment (i.e., Visit 5)

5.1 Preliminary check

```
/* Checking the 'stability' of the model */
PROC MIXED DATA=v4_resid;
```

```
        WHERE _imputation_=1;
        CLASS trt01pn region priortmt ontrt5;
        MODEL v5= resid2 resid3 resid4 trt01pn region priortmt baseline ontrt5
        trt01pn*ontrt5 / SOLUTION;
        LSMEANS trt01pn / DIFFS;
RUN;
```

- Note: if one or more regression coefficients included in the MODEL statement are not estimated successfully or if the estimation of the standard error of the treatment difference is greater than 10 times the size of the estimate of treatment difference, then this algorithm will stop and this imputation techniques will be disregarded. Missing data will then be imputed according to the Copy-Reference approach (see section 14.7).

5.2 Multiple imputation procedure for missing values at Visit 5

```
/* Impute last planned post-baseline assessment (e.g., Visit 5) if missing data at Visit 5 */
PROC MI DATA=v4_resid SEED=14823 NIMPUTE=1 OUT=v5_imputed NOPRINT;
        BY _imputation_;
        CLASS trt01pn region priortmt ontrt5;
        VAR trt01pn region priortmt baseline resid2 resid3 resid4 ontrt5 v5;
        MONOTONE REG (v5= resid2 resid3 resid4 trt01pn region priortmt baseline ontrt5
        trt01pn*ontrt5 / DETAILS);
RUN;
```

5.3 Identify and flag missing data imputed at all visits for subjects who withdraw from study (i.e., monotone missing only – NO intermittent missing)

```
/* Flag imputed monotone missing (only) – NO intermittent missing */
PROC SQL;
        CREATE TABLE v5_imputed_fl
        AS SELECT    a.*,
                        CASE WHEN a.v2 NE b.v2 THEN "Y" ELSE "" END AS impfl2,
                        CASE WHEN a.v3 NE b.v3 THEN "Y" ELSE "" END AS impfl3,
                        CASE WHEN a.v4 NE b.v4 THEN "Y" ELSE "" END AS impfl4,
                        CASE WHEN a.v5 NE b.v5 THEN "Y" ELSE "" END AS impfl5
        FROM v5_imputed AS a
        LEFT JOIN monotone AS b ON a._imputation_=b._imputation_ AND
        a.usubjid=b.usubjid
        ORDER BY _imputation_, usubjid
;QUIT;
```

Step 6: Run ANCOVA Analysis or Logistic Regression on Imputed Data

For ANCOVA Analysis, derive the change from baseline of the given endpoint and then perform the same code as per section 14.1 with the following changes:

```
/* ANCOVA model */
ODS OUTPUT LSMESTIMATES= LSMEstimates LSMEANS=LSMeans;
PROC MIXED DATA = v5_imputed_fl METHOD=REML ALPHA=0.05;
        BY _imputation_;
        ....
RUN;
```

For Logistic Regression, derive the responder flag of the given endpoint and then perform the same code as per section 14.2 with the following changes:

```
/* Logistic Regression model */
ODS OUTPUT ESTIMATES = lgsodds;
PROC GENMOD DATA = v5_imputed_fl;
        BY _imputation_;
        ...
RUN;
```

Step 7: Combining estimates from each imputed data set

For ANCOVA Analysis only.

Combine results according to Rubin's rules

```
/* Rubin's rules to combine estimates by ANCOVA model */
ODS OUTPUT PARAMETERESTIMATES= miparm_diff;
PROC MIANALYZE DATA= LSMEstimates;
        MODELEFFECTS estimate;
        STDERR stderr;
RUN;

ODS OUTPUT PARAMETERESTIMATES= miparm_means;
PROC MIANALYZE PARMS(CLASSVAR=FULL)= LSMeans;
        CLASS trt01pn;
        MODELEFFECTS trt01pn;
RUN;
```

For Logistic Regression only.

Keep log-estimations from Step 6 and combine results according to Rubin's rules

```
/* Estimates by Logistic Regression model on the log-scale */
DATA lgsodds; SET lgsodds;
        WHERE label = " CHF 1535 vs CHF 718";
        KEEP _imputation_ lbetaestimate stderr;
RUN;

/* Rubin's rules to combine estimates by Logistic Regression model */
ODS OUTPUT PARAMETERESTIMATES = lgsodds_myanalyze;
PROC MIANALYZE DATA = lgsodds;
        MODELEFFECTS lbetaestimate;
        STDERR stderr;
RUN;

/* Combine estimates saved */
DATA lgsodds_myanalyze; SET lgsodds_myanalyze;
        pooled_or = EXP(estimate);
        pooled_or_lcl = EXP(LCLMean);
        pooled_or_ucl = EXP(UCLMean);
        KEEP pooled_or pooled_or_lcl pooled_or_ucl;
RUN;
```

Notes:

- Rubin's rules to be applied on the estimations on the log-scale.
- *pooled_*or represents the final estimation of odds ratio after the multiple imputation procedure.
- *pooled_or_lcl* and *pooled_or_ucl* represent, respectively, the final estimation of 95% lower and upper limit of odds ratio after the multiple imputation procedure.

14.7 Imputation of Monotone Missing Data Using Copy Reference Approach

As preliminary note, this is just an example which will need to be adapted considering the relevant visit / inter-visit periods for the analyzed endpoint and *dataset* should contain:

- one row per each subject;
- the values of selected efficacy parameter collected at each post-baseline visit (i.e., *V2, V3, V4* and *V5*) reported as different columns;
- for each planned post-baseline assessment, an indicator variable (i.e., *ONTRT2, ONTRT3, ONTRT4, ONTRT5*) in order to identify if the assessment is on-treatment (i.e., *ONTRT2-ONTRT5* = 1) or off-treatment (i.e., *ONTRT2-ONTRT5* = 0). These indicator variables will be always populated, regardless of whether the assessment is collected or not;
- Treatment (i.e., 1="CHF 1535" and 2="CHF 718") and other relevant covariates.

Below an example of the structure of the starting dataset.

USUBJID	TRT01PN	V2	V3	V4	V5	ONTRT2	ONTRT3	ONTRT4	ONTRT5
1	1	CON	CON	CON	COFF	1	1	1	0
2	2	CON	CON	CON	NCON	1	1	1	1
3	1	CON	CON	COFF	COFF	1	1	0	0

Note: CON = Value collected while on-treatment; COFF = Value collected while off-treatment; NCON = Value not collected while on-treatment; NCOFF = Value not collected while off-treatment

Step 1: Applying Monotone Pattern (step applicable only in case of intermittent missing data, otherwise step should be skipped)

See section 14.5.

Step 2.1: Impute all Monotone Missing Data Under MAR Assumption

(if Step 1 was NOT performed)

```
/* Impute monotone missing data using a MAR approach if no-intermittent missing data
imputed (imputed values for missing off-treatment data will not be retained, see Step 2.3) */
PROC MI DATA=dataset SEED=14823 NIMPUTE=1000 OUT=complete;
        CLASS trt01pn region priortmt;
        VAR trt01pn region priortmt baseline v2 v3 v4 v5;
        MONOTONE REG;
RUN;
```

(if Step 1 was performed)

```
/* Impute monotone missing data using a MAR approach if intermittent missing data imputed
(imputed values for missing off-treatment data will not be retained, see Step 2.3) */
PROC MI DATA=monotone SEED=14823 NIMPUTE=1 OUT=complete;
        BY _imputation_;
        CLASS trt01pn region priortmt;
        VAR trt01pn region priortmt baseline v2 v3 v4 v5;
```

```
        MONOTONE REG;
RUN;
```

Step 2.2: Identify and Flag Off-Treatment Missing Data Imputed at all Visits for Subjects who Withdraw from Study

(if Step 1 was NOT performed)

```
/* Flag imputed monotone missing if no-intermittent missing data imputed */
PROC SQL;
        CREATE TABLE complete_impfl
        AS SELECT    a.*,
                CASE WHEN a.v2 NE b.v2 THEN "Y" ELSE "" END AS impfl2,
                CASE WHEN a.v3 NE b.v3 THEN "Y" ELSE "" END AS impfl3,
                CASE WHEN a.v4 NE b.v4 THEN "Y" ELSE "" END AS impfl4,
                CASE WHEN a.v5 NE b.v5 THEN "Y" ELSE "" END AS impfl5
        FROM complete AS a
        LEFT JOIN dataset AS b ON a.usubjid=b.usubjid
        ORDER BY usubjid;
QUIT;
```

(if Step 1 was performed)

```
/* Flag imputed monotone missing if intermittent missing data imputed – NO flag for
intermittent missing */
PROC SQL;
        CREATE TABLE complete_impfl
        AS SELECT    a.*,
                CASE WHEN a.v2 NE b.v2 THEN "Y" ELSE "" END AS impfl2,
                CASE WHEN a.v3 NE b.v3 THEN "Y" ELSE "" END AS impfl3,
                CASE WHEN a.v4 NE b.v4 THEN "Y" ELSE "" END AS impfl4,
                CASE WHEN a.v5 NE b.v5 THEN "Y" ELSE "" END AS impfl5
        FROM complete AS a
        LEFT JOIN monotone AS b
                        ON a._imputation_=b._imputation_ AND a.usubjid=b.usubjid
        ORDER BY _imputation_, usubjid;
QUIT;
```

Step 2.3: Set Imputed Off-Treatment Data for Test Treatment Group to Missing

```
/* Set the previously imputed values of off-treatment missing data in the test treatment group
to missing */
DATA dataset_CR;
        SET complete_impfl;
        IF trt01pn=1 THEN DO;
                IF ontrt2 ne 1 AND impfl2="Y" THEN v2=.;
                IF ontrt3 ne 1  AND impfl3="Y" THEN v3=.;
                IF ontrt4 ne 1  AND impfl4="Y" THEN v4=.;
                IF ontrt5 ne 1  AND impfl5="Y" THEN v5=.;
        END;
RUN;
```

Step 3: Achieve Control-Based Copy-Reference Imputation for Off-Treatment Missing Data of the Test Treatment Group

Impute missing data under MNAR assumption;

```
/* Impute monotone missing data using a MNAR approach for off-treatment missing data in the test treatment group */
PROC MI DATA= dataset_CR SEED=14823 NIMPUTE=1 OUT=outm1;
        CLASS trt01pn region priortmt;
        BY _imputation_;
        VAR region priortmt baseline v2 v3 v4 v5;
        MONOTONE REG;
        MNAR MODEL (v2 v3 v4 v5/ MODELOBS = (trt01pn = '2'));
RUN;
```

Notes:

- Coefficients in the MODELOBS option of PROC MI to be adapted according to the values of the reference treatment collected in *trt01pn* (2 in the example represents CHF 718);
- (for ANCOVA only – after Step 3 and before entering Step 4) Transpose *outm1* dataset to achieve one record per subject per parameter per visit per imputation to be entered into the model at Step 4. *V2 v3 v4 v5* will be transposed into *change* variable. Merge back the corresponding *avisit* and *avisitn* variables;
- (for Logistic Regression only – after Step 3 and before entering Step 4) Calculate the response flag (e.g., change from baseline on pre-dose morning $FEV_1 \geq 100$ mL) upon imputed data.

  DATA *outm1*; SET *outm1*;
  IF *v5* >= 0.1 THEN *response* = *"Y"*;
  ELSE *response* = *"N"*;
  RUN;

Step 4: Run ANCOVA Analysis or Logistic Regression on Complete Imputed Data

For ANCOVA Analysis, perform the same code as per section 14.1 with the following changes:

```
/* ANCOVA model */
ODS OUTPUT LSMESTIMATES= LSMEstimates LSMEANS=LSMeans;
PROC MIXED DATA = outm1;
        BY _imputation_;
        ....
RUN;
```

For Logistic Regression, perform the same code as per section 14.2 with the following changes:

```
/* Logistic Regression model */
ODS OUTPUT LSMESTIMATES = lgsodds;
PROC GENMOD DATA = outm1;
        BY _imputation_;
        ...
RUN;
```

Step 5: Combining estimates from each imputed data set

For ANCOVA Analysis only.

Combine results according to Rubin's rules

```
/* Rubin's rules to combine estimates by ANCOVA model */
ODS OUTPUT PARAMETERESTIMATES= miparm_diff;
PROC MIANALYZE DATA= LSMEstimates;
        MODELEFFECTS estimate;
        STDERR stderr;
RUN;

ODS OUTPUT PARAMETERESTIMATES= miparm_means;
PROC MIANALYZE PARMS(CLASSVAR=FULL)= LSMeans;
        CLASS trt01pn;
        MODELEFFECTS trt01pn;
RUN;
```

For Logistic Regression only.

Keep log-estimations from Step 4 and combine results according to Rubin's rules

```
/* Estimates by Logistic Regression model on the log-scale */
DATA lgsodds; SET lgsodds;
        WHERE label = " CHF 1535 vs CHF 718";
        KEEP _imputation_ lbetaestimate stderr;
RUN;

/* Rubin's rules to combine estimates by Logistic Regression model */
ODS OUTPUT PARAMETERESTIMATES = lgsodds_myanalyze;
PROC MIANALYZE DATA = lgsodds;
        MODELEFFECTS estimate;
        STDERR stderr;
RUN;

/* Combined estimates saved */
DATA lgsodds_myanalyze; SET lgsodds_myanalyze;
        pooled_or = EXP(estimate);
        pooled_or_lcl = EXP(LCLMean);
        pooled_or_ucl = EXP(UCLMean);
        KEEP pooled_or pooled_or_lcl pooled_or_ucl;
RUN;
```

Notes:

- Rubin's rules to be applied on the estimations on the log-scale.
- *pooled_or* represents the final estimation of odds ratio after the multiple imputation procedure.
- *pooled_or_lcl* and *pooled_or_ucl* represent, respectively, the final estimation of 95% lower and upper limit of odds ratio after the multiple imputation procedure.

14.8 Sensitivity Analysis Using the Tipping-point Approach

The starting point is a complete dataset of 1000 imputations, stemming from either the off-treatment data imputation approach (see step 5.3 from section 14.6) or the copy-reference approach (see step 3 from section 14.7).

The *dataset* should contain, at minimum:

- one row per each subject;
- the imputation counter/id (i.e., *_imputation_*);
- the planned treatment arm *trt01pn* (numeric – 2 levels, 1="CHF 1535" vs. 2="CHF 718") representing the randomized treatment group;
- the (numeric) values of selected efficacy parameter collected/imputed at each post-baseline visit (i.e., *v2, v3, v4* and *v5*) reported as different columns;
- for each planned post-baseline assessment, an indicator variable (i.e., *impfl2, impfl3, impfl4, impfl5*) in order to identify if the value was:
    - a missing value from a discontinued subject imputed with either off-treatment data approach or copy-reference approach (i.e., *impfl2-impfl5* = Y),
    - either an observed value or a missing intermittent value imputed under MAR assumption (i.e., *impfl2-impfl5* = missing);
- other relevant covariates (i.e., *baseline* [numeric] corresponding to the baseline value of the selected efficacy parameter and the stratification factors: *region* and *priortmt*).

Below an example of the structure of the starting dataset.

IMPUTATION	USUBJID	TRT01PN	BASELINE	V2	V3	V4	V5	IMPFL2	IMPFL3	IMPFL4	IMPFL5
1	1	1	xx	xx	xx	xx	xx				
2	2	2	xx	xx	xx	xx	xx			Y	Y
3	3	1	xx	xx	xx	xx	xx				Y

Step 1 & Step 5: Initialize empty datasets and set "delta" values

```
/* MACRO to increment an arbitrary shift value (i.e., delta) within a range to the previous
imputed data */
%MACRO
tipping(shift_min_t=,shift_max_t=,shift_by_t=,shift_min_c=,shift_max_c=,shift_by_c=);

    DATA miparm_comb;
        SET _NULL_;
    RUN;

    %DO i=&shift_min_t. %TO &shift_max_t. %BY &shift_by_t.;
        %DO j=&shift_min_c. %TO &shift_max_c. %BY &shift_by_c.;
```

Notes:

- i (numeric) represents delta value (L) for the planned treatment group CHF 1535 ranging from shift_min_t to shift_max_t by increment shift_by_t (to be defined in the macro call);

- j (numeric) represents delta value (L) for the planned treatment group CHF 718 ranging from shift_min_c to shift_max_c by increment shift_by_c (to be defined in the macro call).

Step 2: Addition of "delta" adjustment to imputed missing values of subjects who prematurely withdraw from study

/ Iteratively save all results by increment an arbitrary shift value (i.e., delta) within a range to the previous imputed data */*

```
DATA outmi;
SET dataset;
        IF trt01pn=1 THEN DO;
                IF impfl5="Y" THEN v5=v5+&i.;
        END;
        IF trt01pn=2 THEN DO;
                IF impfl5="Y" THEN v5=v5+&j.;
        END;
        chg = v5 – base;
RUN;
```

Notes:

- Derive *chg* variable as the change from baseline at Visit 5 (i.e., Week 12);

Step 3: Run ANCOVA analysis on "delta"-adjusted data

Perform similar code as per section 14.1.

/ ANCOVA model */*

```
ODS EXCLUDE ALL;
ODS OUTPUT LSMESTIMATES= LSMEstimates;
PROC MIXED DATA = outmi;
        BY _imputation_;
        CLASS trt01pn region priortmt;
        MODEL chg = trt01pn region priortmt baseline;
        LSMEANS trt01pn / OM CL;
        LSMESTIMATE trt01pn "CHF 1535 vs CHF 718" 1 -1 / CL ;
RUN;
ODS EXCLUDE NONE;
```

Step 4: Combining results

Combine results according to Rubin's rules

/ Rubin's rules to combine estimates by ANCOVA model */*

```
ODS EXCLUDE ALL;
ODS OUTPUT PARAMETERESTIMATES= miparm;
PROC MIANALYZE DATA= LSMEstimates;
        MODELEFFECTS estimate;
        STDERR stderr;
RUN;
ODS EXCLUDE NONE;
```

Step 6: Combining estimates from the steps above and identifying the tipping-points for the delta shift parameters

```
/* Identifying the tipping-points for the delta shift parameters */
                    DATA miparm_comb;
                        SET miparm_comb miparm (IN=a);
                        IF a THEN DO;
                            CHF1535_delta = &i.;
                            CHF718_delta = &j.;
                        END;
                    RUN;
                %END;
            %END;

            PROC FORMAT;
            VALUE signif
                0 = 'CHF718 in favour'
                1 = 'CHF1535 in favour NOT statistically significant'
                2 = 'CHF1535 in favour and statistically significant';
            RUN;
            DATA tipping_point;
                SET miparm_comb;
                IF estimate le 0 THEN signif=0;
                IF estimate gt 0 THEN DO;
                    IF probt ge 0.05 THEN signif=1;
                    ELSE signif=2;
                END;
            RUN;
            PROC PRINT DATA=tipping_point NOOBS;
                WHERE signif=1;
            RUN;
```

(graphical representation of results #1)

```
/* Plot of statistically significant */
            ODS GRAPHICS ON;
            PROC SGPLOT DATA=tipping_point;
            /*Define the colors and the symbol of the "signif" defined later*/
                STYLEATTRS
                DATACONTRASTCOLORS=(RED ORANGE GREEN)
                DATASYMBOLS=(CIRCLEFILLED);
            /* Plot the data */
                SCATTER X= CHF1535_delta Y= CHF718_delta /
                    MARKERATTRS=(SIZE=14) GROUP=signif;
            /* X-axis options*/
                XAXIS
                LABEL=" Delta (mL) In CHF1535 Arm"
                LABELATTRS=(FAMILY=VERDANA COLOR=BLACK SIZE=10)
                DISPLAY=(NOTICKS)
                VALUES=(&shift_min_t. TO &shift_max_t.  BY &shift_by_t. )
                GRID
```

```
        OFFSETMIN=0.05
        OFFSETMAX=0.05;
    /* Y-axis options*/
        YAXIS
        LABEL=" Delta (mL) In CHF718 Arm"
        LABELATTRS=(FAMILY=VERDANA COLOR=BLACK SIZE=10)
        DISPLAY=(NOTICKS)
        VALUES=(&shift_min_c.  TO &shift_max_c.  BY &shift_by_c. )
        GRID
        OFFSETMIN=0.10
        OFFSETMAX=0.10;
    /* Plot title */
        TITLE "Two-dimensional Tipping Point Analysis";
        TITLE2 "Plot of Statistical Significance";
        FORMAT signif.;
        LABEL signif='00'X;
    RUN;
    ODS GRAPHICS OFF;
```

(

%MEND tipping;

Step 7: *tipping* macro call

```
/* Call macro tipping */
%tipping(   shift_min_t=-1,shift_max_t=0,shift_by_t=0.05,
            shift_min_c=-1,shift_max_c=0,shift_by_c=0.05);
```

15 References

1. Chiesi Farmaceutici S.p.A. TLFs_Library_v1.0_signed. 10 Sep 2019.
2. Chiesi Farmaceutici S.p.A. Instructions for Producing Statistical Analysis Plan & Statistical Output. 25 Jan 2016.
3. ICH E9: Statistical Principles for Clinical Trials. Sept 1998.
4. ICON BST004-SOP Statistical Analysis Plan v3.0.
5. AQLQ Background October 2018.pdf.
6. Dweik at al. ATS FeNO guidelines AJRCCM 2011.
7. Hankinson et al. Use of forced vital capacity and forced expiratory volume in 1 second quality criteria for determining a valid test Eur Respir J 2015 May;45(5):1283-92.
8. Roger JH, Bratton DJ, Mayer B, et al. Treatment policy estimands for recurrent event data using data collected after cessation of randomised treatment. Pharm Stat. 2019 Jan;18(1):85-95.
9. Casey et al .2021, Estimand framework: Are we asking the right questions? A case study in the solid tumor setting, Pharmaceutical Statistics. 2021;20:324–334.
10. Fagerland MW, Lydersen S, Laake P. Recommended confidence intervals for two independent binomial proportions. Stat Methods Med Res. 2015 Apr;24(2):224-54. Doi: 10.1177/0962280211415469. Epub 2011 Oct 13. PMID: 21996567.
11. Ratitch B, O'Kelley M, and Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharmaceutical Statistics, 2013; 12: 337-347.
12. Roger J (2022) Stepwise imputation for marginal model based on previous residuals, (commented SAS code) available at https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-missing-data.
13. O'Kelly M and Li S (2022) Template code treatment policy estimand using SAS PROC MI and the MISTEP macro, (commented SAS code) available at https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-missing-data.
14. United States Census Bureau, Geography Division. "Census Regions and Divisions of the United States", available at https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf.

16 List of Tables, Listings and Figures

16.1 Tables

The SAS output for the analyses included in the flagged (***) tables below will be provided for internal use only and not for inclusion into the CSR.

For the final analysis, in case the same table is planned for Safety and ITT set, if the Safety and ITT sets are equal, the tables on the Safety set will not be presented.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.1.1	Screen Failures and Reasons (Enrolled Set)	DST001	- Only overall column should be displayed. - Reasons for screen failure should be reported by decreasing overall frequency.	Source: Listing 16.2.1.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.1.2	Disposition by Treatment (Randomized Set)	DST002	- Overall column should be displayed. - Reasons for discontinuation/withdrawal should be reported by decreasing overall frequency. - Display the following rows: - Completed the study. - Withdrew from the study (with reasons of withdrawal). - Completed the study treatment. - Discontinued the study treatment (with reasons for treatment discontinuation). - Discontinued the study treatment (with reasons for treatment discontinuation), allowed to remain in the study and completed all the planned the study visits. - Discontinued the study treatment (with reasons for treatment discontinuation), allowed to remain in the study and did not complete all the planned the study visits. - Discontinued the study treatment (with reasons for treatment discontinuation/study Withdrew) and withdrew the study at the same time	Source: Listing 16.2.1.2

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.1.3	Disposition by Region and Site (Randomized Set)	DST004	- Overall columns should be displayed. - Present Region and Site within each Region in the first column (Region sorted by Alphabetic order Site sorted by ascending value). - Display overall the region count and then by site. - Display the following rows: - Randomized - Randomized and treated - Randomized and not treated - Completed the Treatment - Discontinued the Treatment - Completed the Study - Discontinued the Study	Source: Listing 16.2.1.2
Table 14.1.1.4.1	Time to Discontinuation from the Study Treatment (Randomized Set)	Not available	Columns to display (repeat the time block for each treatment group): - Time (Weeks): [0-4), [4-8), [8-EoT] - Number of Subjects in Study at the Beginning of the Period - Cumulative Number of Discontinued Subjects at the End of the Period - Probability of Discontinuation at the End of the Period	Source: Listing 16.2.1.2 Footnotes: [1] EoT = End of Treatment period. [2] Subjects who complete the study are considered as 'Censored' at the last day in the study. [3] Results obtained from Kaplan-Meier (KM) analysis. [4] Time to discontinuation from the study treatment (weeks) = (date of study treatment completion/discontinuation – date of start of randomized treatment period + 1) / 7.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.1.4.2	Time to Discontinuation from the Study (Randomized Set)	Not available	Columns to display (repeat the time block for each treatment group): - Time (Weeks): [0-4), [4-8), [8- 12), [12-EoS] - Number of Subjects in Study at the Beginning of the Period - Cumulative Number of Discontinued Subjects at the End of the Period - Probability of Discontinuation at the End of the Period	Source: Listing 16.2.1.2 Footnotes: [1] EoS = End of Study Period. [2] Subjects who complete the study are considered as 'Censored' at the last day in the study. [3] Results obtained from Kaplan-Meier (KM) analysis. [4] Time to discontinuation from the study treatment (weeks) = (date of study treatment completion/discontinuation – date of start of randomized treatment period + 1) / 7.
Table 14.1.1.5	Attendance at Study Visits (Randomized Set)	SVT001	- Overall column should be displayed. - Display visits as per section 13.2.1. - Display as follow (display on all rows n and %):Visit 0 (Week -3) Visit 1 (Week -2) Visit 2 (Week 0, Day 1) to Visit 5 (Week 12) On-treatment [1] Off-treatment [2] Visit 6 (Week 13 – FU)	Source: Listing 16.2.1.4 Footnotes: [1] The on-treatment period is defined as the period between the date of first randomized study medication intake and the date of last randomized study medication intake. [2] The off-treatment period, in case subject accepts to attend post-treatment visits, is defined as the period between the day after the date of last randomized study medication intake and the date of study conclusion. [3] FU = Follow-up

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.1.6	Analysis Sets (Randomized Set)	DST005	- Overall column should be displayed. - Populations to be displayed: Safety [1] and ITT Sets [2].	Source: Listing 16.2.3.1 Footnotes: [1] The Safety set includes all randomized subjects who receive at least one dose of study treatment (analyzed as treated). [2] The Intention-to-Treat (ITT) set includes all randomized subjects who receive at least one dose of the study treatment (analyzed as randomized).
Table 14.1.1.7	Important Protocol Deviations (Intention-To-Treat Set)	DVT001	- Overall column should be displayed. - Deviation Category and Deviation Type should be displayed by decreasing frequency.	Source: Listing 16.2.2.1
Table 14.1.2	Baseline Characteristics (Intention-To-Treat Set)	DMT001	- Overall column should be displayed. - All categories to be displayed even if empty. - Present the following parameters: - Age (years) - Age Category (<65; >= 65) - Sex - Race [in case of multiple races, category 'multiple' will be added to table] - Ethnicity - Region - Baseline Height (cm) - Baseline Weight (kg) - Baseline BMI (kg/m^2) [1]	Source: Listing 16.2.4.1 Footnotes: [1] Baseline BMI has been calculated as weight (kg) / height (m^2). [2] A subject can be counted in several categories of race.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.3	Asthma History (Intention-To-Treat Set)	SCT001	- Overall column should be displayed. - Present the following parameters: - Time Since First Diagnosis (Months) [1] - Asthma Medication Category at Study Entry [ICS/LABA combination (i.e., ICS/LABA fixed combination, ICS + LABA free combination), high dose ICS and medium dose ICS] [2] - Number of Asthma Exacerbations in the 4 weeks before Screening (categories 0 or 1+) - Time Since Last Documented Exacerbation - Treatment of the Most Recent Exacerbation (Systemic Corticosteroids, Hospitalization, Emergency Room) [2].	Source : Listing 16.2.4.3 Footnotes: [1] Time since first diagnosis (months) have been calculated as (Visit 1 date – First diagnosis date + 1) /30.4375. [2] A subject can be counted in several categories. [3] Time since last documented exacerbation if not ongoing (months) have been calculated as (Date of Visit 1 – Date of last exacerbation) / 30.4375.
Table 14.1.4	Smoking Status (Intention-To-Treat Set)	SUT001	- Overall column should be displayed. - Present the following parameters: **Tobacco Products** *as a sub-header* - Smoking Status at Screening - Duration of Smoking (years) [1] - Number of Pack-years **Electronic Cigarettes** *as a sub-header* - Smoking Status at Screening - Duration of Smoking (years) [1] - Type (nicotine based; not nicotine based)	Source: Listing 16.2.4.2 Footnote: [1] For ex-smokers, duration of smoking (years) = (stop date – start date + 1) / 365.25.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.5	Spirometry and Reversibility Test (Intention-to-Treat Set)	RET001	- Overall column should be displayed. - Variables to be presented are: - Pre-bronchodilator at Visit 1 (Week -2) *as a sub header* - FEV_1 (L) - FVC (L) - FEV_1 Predicted (%)- Post- bronchodilator at Visit 1 (Week -2) *as a sub header* - FEV_1 (L) - FVC (L) - FEV_1 Predicted (%) - Pre-dose at Visit 2 (Week 0, Day 1) *as a sub header* - FEV_1 (L) - FVC (L)	Source: Listings 16.2.4.4, 16.2.6.1.1 to 16.2.6.1.4
Table 14.1.6	Rescue Medication Use During Run-in Period (Intention-To-Treat Set)	XRT001	- Overall column should be displayed. - Include summary statistics for the following parameters: - Percentage of Rescue Medication-free Days (%) [2] - Average Rescue Medication Use (puffs/day) [3]	Source: Listing 16.2.6.5 Footnotes: [1] Rescue Medication Use (if no rescue medication recorded then the subject is counted in the No category [2] Percentage of rescue medication-free days = 100 * (number of rescue medication-free days during run-in period / number of days on which daily rescue medication use is assessed during the run-in period). A rescue medication-free day is a day with a sum of puffs of rescue medication = 0. [3] Average number of puffs/day = total number of puffs of rescue medication during the run-in period / Number of days on which daily rescue medication use is assessed during the run-in period. [4] Only data from eDiary are included.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.7.1	Medical and Surgical History (Intention-to-Treat Set)	MHT001	- Overall column should be displayed. - To be presented by System Organ Class and then by Preferred Term, alphabetically sorted.	Source: Listing 16.2.4.6 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version XX.X.'
Table 14.1.7.2	Concomitant Diseases (Intention-to-Treat Set)	MHT001	Same as Table 14.1.7.2	Source: Listing 16.2.4.7 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA Version XX.X.'
Table 14.1.8.1.1	Prior Medications (Intention-to-Treat Set)	CMT001	- Overall column should be displayed. - Table will be presented by Anatomical Main Group (1st level ATC), Therapeutic Subgroup (2nd level ATC), Chemical Subgroup (4th level ATC) and preferred name, alphabetically sorted.	Source: Listing 16.2.4.9.1, Listing 16.2.4.9.2 Footnote: [1] ATCs and Preferred Names are coded using WHO-DD Global B3 March XXXX.
Table 14.1.8.1.2	Concomitant and Post-Treatment Medications (Intention-to-Treat Set)	CMT002	Same as Table 14.1.8.1.1	Same as Table 14.1.8.1.1
Table 14.1.8.2.1	Prior Asthma Medications (Intention-to-Treat Set)	CMT001	Same as Table 14.1.8.1.1	Source: Listing 16.2.4.9.1 Footnote: [1] ATCs and Preferred Names are coded using WHO-DD Global B3 March XXXX.
Table 14.1.8.2.2	Prior Non-Asthma Medications (Intention-to-Treat Set)	CMT001	Same as Table 14.1.8.1.1	Source: Listing 16.2.4.9.2 Footnote: [1] ATCs and Preferred Names are coded using WHO-DD Global B3 March XXXX.
Table 14.8.3.1	Concomitant Asthma Medications (Intention-to-Treat Set)	CMT002	Same as Table 14.1.8.1.1	Source: Listing 16.2.4.9.1 [1] ATCs and Preferred Names are coded using WHO-DD Global B3 March XXXX.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.8.3.2	Concomitant Non-Asthma Medications (Intention-to-Treat Set)	CMT002	Same as Table 14.1.8.1.1	Source: Listing 16.2.4.9.2 Footnote: [1] ATCs and Preferred Names are coded using WHO-DD Global B3 March XXXX.
Table 14.1.8.4.1	Post-treatment Asthma Medications (Intention-to-Treat Set)	CMT002	Same as Table 14.1.8.1.1	Source: Listing 16.2.4.9.1 [1] ATCs and Preferred Names are coded using WHO-DD Global B3 March XXXX.
Table 14.1.8.4.2	Post-treatment Non- Asthma Medications (Intention-to-Treat Set)	CMT002	Same as Table 14.1.8.1.1	Source: Listing 16.2.4.9.2 Footnote: [1] ATCs and Preferred Names are coded using WHO-DD Global B3 March XXXX.
Table 14.1.9.1	Prior Procedures (Intention-To-Treat Set)	MHT001	- Overall column should be displayed. - To be presented by System Organ Class and then by Preferred Term, alphabetically sorted.	Source: Listing 16.2.4.8 Footnote: [1] System Organ Class and Preferred Term are coded using MedDRA version XX.X'
Table 14.1.9.2	Concomitant or Post-Treatment Procedures (Intention-To-Treat Set)	MHT002	Same as Table 14.1.9.1	Same as Table 14.1.9.1

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.10.1	Treatment Compliance during Run-In Period (Intention-To-Treat Set)	EXT002	Present descriptive statistics for compliance. Present frequency and percentage for categories of compliance: • [0%-10%), [10%-20%), [20%-30%), [30%-40%), [40%-50%), [50%-60%), [60%-70%), [70%-80%), [80%-90%), [90%-100%), [100%-135%], and >135%. • <50% and >=50%	Source : Listing 16.2.5.1 Footnotes: [1] Treatment Compliance = (Total number of administered doses/ Total number of scheduled doses) x 100. [2] Total number of administered doses = Total number of inhalations recorded from the evening eDiary session of the day of Visit 1 (including morning data collected in eCRF if available) to the morning eDiary session of the day of start of randomized treatment period (reporting the dose taken the evening before), inclusive. [3] Total number of scheduled doses = [(Date of start of randomized treatment period) – (Date of Visit 1)] * x, where x= if the screened subject was put on CHF 718 pMDI 100μg 2 inhalations BID (TDD 400 μg) OR x=8, if the screened subject was put on CHF 718 pMDI 100μg 4 inhalations BID (TDD 800 μg) during the 2-week run in period.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.10.2	Treatment Compliance during Treatment Period (Intention-To-Treat Set)	EXT002	Present descriptive statistics for compliance. Present frequency and percentage for categories of compliance. Three categorical label should be display one for each categories of compliance: • [0%-10%), [10%-20%), [20%-30%), [30%-40%), [40%-50%), [50%-60%), [60%-70%), [70%-80%), [80%-90%), [90%-100%), [100%-135%], and >135%. • 65%, [65% - 135%] and >135%.	Source : Listing 16.2.5.3 Footnotes: [1] Treatment Compliance = (Total number of administered doses/ Total number of scheduled doses) x 100. [2] Total number of administered doses = Total number of inhalations performed from the evening eDiary session of the day of first randomized study medication intake (including morning data collected in eCRF if available) to the day of last randomized study medication intake, inclusive. [3] If date of last randomized medication intake < date of Visit 5 (Week 12): Total number of scheduled doses = [(Date of last randomized medication intake) – (Date of first randomized medication intake) + 1] * 8. If the date of last randomized medication intake = date of Visit 5 (Week 12): Total number of scheduled doses = (Date of last randomized medication intake – Date of first randomized medication intake) * 8 + 4.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.1.11	Compliance to the e-Diary (Intention-To-Treat Set)	EXT002	Present descriptive statistics for compliance for both Run-In and Treatment Period. Present frequency and percentage for categories of compliance: 0%-50%), [50%-75%), [75%-100%],	Source : Listing 16.2.6.2 Footnotes: [1] Compliance during the run-in period (%) = [Total number of sessions in the run-in period with data recorded in the diaries / ((Date of start of randomized treatment period – Date of Visit 1)*2)]*100 [2] If the day of end of efficacy assessment period/ discontinuation is the day of a clinic visit: Compliance during the randomized treatment period (%) = [Total number of sessions in the randomized treatment period with data recorded in the diaries / (2*(Date of end of efficacy assessment period/ discontinuation – Date of start of randomized treatment period))]*100. [3] If the day of end of efficacy assessment period/ discontinuation is not the day of a clinic visit: Compliance during the randomized treatment period (%) = [Total number of sessions in the randomized treatment period with data recorded in the diaries / (2*(Date of end of efficacy assessment period/ discontinuation – Date of start of randomized treatment period) + 1)]*100.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.1.1	Summary of Actual and Change from Baseline in FEV_1 $AUC_{0\text{-}12h}$ (L) normalized by time – Main Estimand (Intention-To-Treat Set)	TPT001	- Descriptive statistics will be presented to summarize actual value and change from baseline at visit 2 (Week 0, Day 1) and at visit 5 (Week 12) by treatment group for: FEV_1 $AUC_{0\text{-}12h}$ (L) normalized by time. - Descriptive statistics will include n, Mean (SD) ,95% CI for Mean, Median, Minimum, Maximum. - Data to be considered: include on-treatment and off-treatment data, but not imputed data.	Source: Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] Baseline is defined as the arithmetic mean of the pre-dose FEV_1 measurements (at 45 mins and 15 mins pre-dose) collected at week 0 (Visit 2). [2] FEV_1 $AUC_{0\text{-}12h}$ are calculated using the linear trapezoidal method and then normalized to the length of time. [3] No imputed data displayed
Table 14.2.1.2	Statistical Analysis of Change from Baseline in FEV_1 $AUC_{0\text{-}12h}$ (L) normalized by time at Week 12 – Main Estimand (Intention-To-Treat Set)	ANT001	- ANCOVA model at visit 5 (Week 12) including covariates as detailed in section 7.4 will be performed. - Data to be considered: This statistical analysis will include on-treatment, off-treatment and imputed data. Missing data will be imputed using available off-treatment data (or a CR imputation) as detailed in section 7.3.1.	Source : Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.1.3.1	Statistical Analysis of Change from Baseline in FEV_1 AUC_{0-12h} (L) normalized by time at Week 12 – Main Estimand, Sensitivity Analysis (Intention-To-Treat Set)	Not available	- Analysis to be conducted and displayed only if significant results (i.e.,treatment difference in favor of CHF 1535 arm and p-value < 0.05) is found in the main analysis of the primary endpoint at Table 14.2.1.2. - A 2-way crossed table/shift table presenting: **Rows**: Shift parameter for CHF 1535; **Columns**: Shift parameter for CH718; **Cells**: line#1 Adjusted Mean Difference at Week 12, line#2 p-value. - On the right side of p-value add an indicator * to identify those p-values ≥ 0.05 associated with a mean difference at Week 12 in favour of CHF 1535; and an indicator ** to identify those mean differences at Week 12 not in favour of CHF 1535. - Management of ANCOVA model and of missing data will be the same as the one used for the primary analysis of Table 14.2.1.2.	Source : Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] Treatment difference at Week 12 and p-value estimed by means of ANCOVA model including treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation). [3] Two-dimensional tipping point run with shift parameters for CHF 1535 and CHF 718 ranging from -1 to 0 L with increments of 0.05 L. [4] * indicates an estimated treatment difference at Week 12 in favour of CHF 1535 vs. CHF 718, which is not statistically significant (i.e., p-value ≥ 0.05). ** indicates an estimated treatment difference at Week 12 not in favour of CHF 1535 vs. CHF 718
Table 14.2.1.3.2	Statistical Analysis of Change from Baseline in FEV_1 AUC_{0-12h} (L) normalized by time at Week 12 – Sensitivity Analysis of High Rate of Misclassification of Prior Asthma Therapy (Intention-To-Treat Set)		Same as Table 14.2.1.2.	Same as Table 14.2.1.2. Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy (recorded in IWRS) as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.1.3.3	Statistical Analysis of Change from Baseline in FEV_1 AUC_{0-12h} (L) normalized by time at Week 12 – Sensitivity Analysis of Patients Randomized More than Once with Overlapping Study Periods (Intention-To-Treat Set)		Same as Table 14.2.1.2.	Same as Table 14.2.1.2. [3] Patients randomized more than once with overlapping study periods were excluded
Table 14.2.1.4	Statistical Analysis of Change from Baseline in FEV_1 AUC_{0-12h} (L) normalized by time at Week 12 – Main Estimand – Subgroup Analysis: Stratified by Age (Intention-To-Treat Set)	ANT001	Same as Table 14.2.1.2. - Stratifying subgroup variable: Age (<65, ≥65). - Add header row to present statistical analyses for each category. If there are < 20 subjects per category of subgroup, inferential analysis will not be performed on that category and only descriptive summaries will be provided on that category. Note [3] should only be display when n < 20 subjects per category of subgroup.	Same as Table 14.2.1.2. [3] NE - not estimated since n < 20 subjects per category of subgroup.
Table 14.2.1.5	Statistical Analysis of Change from Baseline in FEV_1 AUC_{0-12h} (L) normalized by time at Week 12 – Main Estimand – Subgroup Analysis: Stratified by Sex (Intention-To-Treat Set)	ANT001	Same as Table 14.2.1.2. - Stratifying subgroup variable: Sex (M, F). - Add header row to present statistical analyses for each category. If there are < 20 subjects per category of subgroup, inferential analysis will not be performed on that category and only descriptive summaries will be provided on that category. Note [3] should only be display when n < 20 subjects per category of subgroup.	Same as Table 14.2.1.2. [3] NE - not estimated since n < 20 subjects per category of subgroup.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.1.6	Statistical Analysis of Change from Baseline in FEV_1 AUC_{0-12h} (L) bormalized by time at Week 12 – Main Estimand – Subgroup Analysis: Stratified by BMI (Intention-To-Treat Set)	ANT001	Same as Table 14.2.1.2. - Stratifying subgroup variable: Baseline BMI (<25, 25-30, ≥30). - Add header row to present statistical analyses for each category. If there are < 20 subjects per category of subgroup, inferential analysis will not be performed on that category and only descriptive summaries will be provided on that category. Note [3] should only be display when n < 20 subjects per category of subgroup.	Same as Table 14.2.1.2. [3] NE - not estimated since n < 20 subjects per category of subgroup.
Table 14.2.1.7	Statistical Analysis of Change from Baseline in FEV_1 AUC_{0-12h} (L) normalized by time at Week 12 – Main Estimand – Subgroup Analysis: Stratified by Smoking Status (Intention-To-Treat Set)	ANT001	Same as Table 14.2.1.2. - Stratifying subgroup variable: Baseline Smoking Status (Non-smoker, Ex-smoker). - Add header row to present statistical analyses for each category. If there are < 20 subjects per category of subgroup, inferential analysis will not be performed on that category and only descriptive summaries will be provided on that category. Note [3] should only be display when n < 20 subjects per category of subgroup.	Same as Table 14.2.1.2. [3] NE - not estimated since n < 20 subjects per category of subgroup.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.1.8	Statistical Analysis of Change from Baseline in FEV_1 AUC_{0-12h} (L) normalized by time at Week 12 – Main Estimand – Subgroup Analysis: Stratified by Pre-bronchodilator FEV_1 Predicted at Screening (Intention-To-Treat Set)	ANT001	Same as Table 14.2.1.2. - Stratifying subgroup variable: Pre-bronchodilator FEV_1 Predicted at Screening (Mild: >65%, Moderate: 50-65%, Severe: <50%). - Add header row to present statistical analyses for each category. If there are < 20 subjects per category of subgroup, inferential analysis will not be performed on that category and only descriptive summaries will be provided on that category. Note [3] should only be display when n < 20 subjects per category of subgroup.	Same as Table 14.2.1.2. [3] NE - not estimated since n < 20 subjects per category of subgroup.
Table 14.2.1.9	Statistical Analysis of Change from Baseline in FEV_1 AUC_{0-12h} (L) normalized by time at Week 12 – Main Estimand – Subgroup Analysis: Stratified by Race (Intention-To-Treat Set)	ANT001	Same as Table 14.2.1.2. - Stratifying subgroup variable: Race (White, Black or African American, Other). - Add header row to present statistical analyses for each category. If there are < 20 subjects per category of subgroup, inferential analysis will not be performed on that category and only descriptive summaries will be provided on that category. Note [3] should only be display when n < 20 subjects per category of subgroup.	Same as Table 14.2.1.2. [3] NE - not estimated since n < 20 subjects per category of subgroup.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.1.10	Statistical Analysis of Change from Baseline in FEV_1 AUC_{0-12h} (L) normalized by time at Week 12 – Main Estimand – Subgroup Analysis: Stratified by Race and Ethnicity (Intention-To-Treat Set)	ANT001	Same as Table 14.2.1.2. - Stratifying subgroup variable: Race & ethnicity combined (White/Non-Hispanic, Black/Non-Hispanic, Hispanic). - Add header row to present statistical analyses for each category. If there are < 20 subjects per category of subgroup, inferential analysis will not be performed on that category and only descriptive summaries will be provided on that category. Note [3] should only be display when n < 20 subjects per category of subgroup.	Same as Table 14.2.1.2. [3] NE - not estimated since n < 20 subjects per category of subgroup.
Table 14.2.2.1	Summary of Actual and Change from Baseline in peak FEV_1 (L) within the first 3 hours post-dose – Main Estimand (Intention-To-Treat Set)	TPT001	- Descriptive statistics will be presented to summarize actual value and change from baseline at visit 2 (Week 0, Day 1) and visit 5 (Week 12) by treatment group for: peak FEV_1 (L) within the first 3 hours post-dose. - Descriptive statistics will include n, Mean (SD), 95% CI for Mean, Median, Minimum, Maximum. - Data to be considered: include on-treatment and off-treatment data, but not imputed data.	Source: Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] Baseline is defined as the arithmetic mean of the pre-dose FEV_1 measurements (at 45 mins and 15 mins pre-dose) collected at week 0 (Visit 2). [2] No imputed data displayed
Table 14.2.2.2	Statistical Analysis of Change from Baseline in peak FEV_1 (L) within the first 3 hours post-dose at Week 12 – Main Estimand (Intention-To-Treat Set)	ANT001	- ANCOVA model at visit 5 (Week 12) including covariates as detailed in section 7.4 will be performed. - Data to be considered: This statistical analysis will include on-treatment, off-treatment and imputed data. Missing data will be imputed using available off-treatment data (or a CR imputation) as detailed in section 7.3.1	Source : Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.2.3.1	Statistical Analysis of Change from Baseline in peak FEV_1 (L) within the first 3 hours post-dose at Week 12 –- Main Estimand –- Sensitivity Analysis (Intetion-To-Treat Set)	Not available	Same as Table 14.2.1.3.	Same as Table 14.2.1.3.
Table 14.2.2.3.2	Statistical Analysis of Change from Baseline in peak FEV_1 (L) within the first 3 hours post-dose at Week 12 – Sensitivity Analysis of High Rate of Misclassification of Prior Asthma Therapy (Intention-To-Treat Set)		Same as Table 14.2.2.2.	Same as Table 14.2.2.2. Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy (recorded in IWRS) as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).
Table 14.2.2.3.3	Statistical Analysis of Change from Baseline in peak FEV_1 (L) within the first 3 hours post-dose at Week 12 – Sensitivity Analysis of Patients Randomized More than Once with Overlapping Study Periods (Intention-To-Treat Set)		Same as Table 14.2.2.2.	Same as Table 14.2.2.2. [3] Patients randomized more than once with overlapping study periods were excluded

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.2.4	Statistical Analysis of Change from Baseline in peak FEV_1 (L) within the first 3 hours post-dose at Week 12 – Main Estimand Subgroup Analysis: Stratified by Age (Intention-To-Treat Set)	ANT001	Same as Table 14.2.2.2. - Stratifying subgroup variable: Age (<65, ≥65). - Add header row to present statistical analyses for each category. If there are < 20 subjects per category of subgroup, inferential analysis will not be performed on that category and only descriptive summaries will be provided on that category. Note [3] should only be display when n < 20 subjects per category of subgroup.	Same as Table 14.2.2.2. [3] NE - not estimated since n < 20 subjects per category of subgroup.
Table 14.2.2.5	Statistical Analysis of Change from Baseline in peak FEV_1 (L) within the first 3 hours post-dose at Week 12 – Main Estimand Subgroup Analysis: Stratified by Sex (Intention-To-Treat Set)	ANT001	Same as Table 14.2.2.2. - Stratifying subgroup variable: Sex (M, F). - Add header row to present statistical analyses for each category. If there are < 20 subjects per category of subgroup, inferential analysis will not be performed on that category and only descriptive summaries will be provided on that category. Note [3] should only be display when n < 20 subjects per category of subgroup.	Same as Table 14.2.2.2. [3] NE - not estimated since n < 20 subjects per category of subgroup.
Table 14.2.2.6	Statistical Analysis of Change from Baseline in peak FEV_1 (L) within the first 3 hours post-dose at Week 12 – Main Estimand Subgroup Analysis: Stratified by BMI (Intention-To-Treat Set)	ANT001	Same as Table 14.2.2.2. - Stratifying subgroup variable: Baseline BMI (<25, 25-30, ≥30). - Add header row to present statistical analyses for each category. If there are < 20 subjects per category of subgroup, inferential analysis will not be performed on that category and only descriptive summaries will be provided on that category. Note [3] should only be display when n < 20 subjects per category of subgroup.	Same as Table 14.2.2.2. [3] NE - not estimated since n < 20 subjects per category of subgroup.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.2.7	Statistical Analysis of Change from Baseline in peak FEV_1 (L) within the first 3 hours post-dose at Week 12– Main Estimand Subgroup Analysis: Stratified by Smoking Status (Intention-To-Treat Set)	ANT001	Same as Table 14.2.2.2. - Stratifying subgroup variable: Baseline Smoking Status (Non-smoker, Ex-smoker). - Add header row to present statistical analyses for each category. If there are < 20 subjects per category of subgroup, inferential analysis will not be performed on that category and only descriptive summaries will be provided on that category. Note [3] should only be display when n < 20 subjects per category of subgroup.	Same as Table 14.2.2.2. [3] NE - not estimated since n < 20 subjects per category of subgroup.
Table 14.2.2.8	Statistical Analysis of Change from Baseline in peak FEV_1 (L) within the first 3 hours post-dose at Week 12 – Main Estimand Subgroup Analysis: Stratified by Pre-bronchodilator FEV_1 Predicted at Screening (Intention-To-Treat Set)	ANT001	Same as Table 14.2.2.2. - Stratifying subgroup variable: Pre-bronchodilator FEV_1 Predicted at Screening(Mild: >65%, Moderate: 50-65%, Severe: <50%). - Add header row to present statistical analyses for each category. If there are < 20 subjects per category of subgroup, inferential analysis will not be performed on that category and only descriptive summaries will be provided on that category. Note [3] should only be display when n < 20 subjects per category of subgroup.	Same as Table 14.2.2.2. [3] NE - not estimated since n < 20 subjects per category of subgroup.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.2.9	Statistical Analysis of Change from Baseline in peak FEV_1 (L) within the first 3 hours post-dose at Week 12 – Main Estimand Subgroup Analysis: Stratified by Race (Intention-To-Treat Set)	ANT001	Same as Table 14.2.2.2. - Stratifying subgroup variable: Race (White, Black or African American, Other). - Add header row to present statistical analyses for each category. If there are < 20 subjects per category of subgroup, inferential analysis will not be performed on that category and only descriptive summaries will be provided on that category. Note [3] should only be display when n < 20 subjects per category of subgroup.	Same as Table 14.2.2.2. [3] NE - not estimated since n < 20 subjects per category of subgroup.
Table 14.2.2.10	Statistical Analysis of Change from Baseline in peak FEV_1 (L) within the first 3 hours post-dose at Week 12 – Main Estimand Subgroup Analysis: Stratified by Race and Ethnicity (Intention-To-Treat Set)	ANT001	Same as Table 14.2.2.2. - Stratifying subgroup variable: Race & ethnicity combined (White/Non-Hispanic, Black/Non-Hispanic, Hispanic). - Add header row to present statistical analyses for each category. If there are < 20 subjects per category of subgroup, inferential analysis will not be performed on that category and only descriptive summaries will be provided on that category. Note [3] should only be display when n < 20 subjects per category of subgroup.	Same as Table 14.2.2.2. [3] NE - not estimated since n < 20 subjects per category of subgroup.
Table 14.2.3.1	Statistical Analysis of Change from Baseline in FEV_1 AUC_{0-12h} (L) normalized by time at Week 0 –- Main Estimand (Intention-To-Treat Set)	ANT001	- ANCOVA model at visit 2 (Week 0, Day 1) including covariates as detailed in section 7.4 will be performed - Data to be considered: This statistical analysis will include on-treatment, off-treatment and imputed data. Missing data will be imputed using available off-treatment data (or a CR imputation) as detailed in section 7.3.1.	Source : Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] ANCOVA model include treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.4.1	Statistical Analysis of Change from Baseline in peak FEV_1 (L) within the first 3 hours post-dose at Week 0 –- Main Estimand (Intention-To-Treat Set)	ANT001	- ANCOVA model at visit 2 (Week 0, Day 1) including covariates as detailed in section 7.4 will be performed. - Data to be considered: This statistical analysis will include on-treatment, off-treatment and imputed data. Missing data will be imputed using available off-treatment data (or a CR imputation) as detailed in section 7.3.1.	Source : Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).
Table 14.2.5.1	Summary of Actual and Change from Baseline in trough FEV_1 (L)- Main Estimand (Intenrion-To-Treat Set)	TPT001	- Descriptive statistics will be presented to summarize actual value and change from baseline at visit 2 (Week 0, Day 1) and visit 5 (Week 12) by treatment group for trough FEV_1 (L) - Descriptive statistics will include n, Mean (SD), 95% CI for Mean, Median, Minimum, Maximum. - Data to be considered: include on-treatment and off-treatment data, but not imputed data.	Source: Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] Baseline is defined as the arithmetic mean of the pre-dose FEV_1 measurements (at 45 mins and 15 mins pre-dose) collected at week 0 (Visit 2). [2] No imputed data displayed
Table 14.2.5.2	Statistical Analysis of Change from Baseline in trough FEV_1 (L) at Week 12 (Intention-To-Treat Set) Main Estimand	ANT001	- ANCOVA model at visit 2 (Week 0, Day 1) and visit 5 (Week 12) including covariates as detailed in section 7.4 will be performed. - Data to be considered: This statistical analysis will include on-treatment, off-treatment and imputed data. Missing data will be imputed using available off-treatment data (or a CR imputation) as detailed in section 7.3.1.	Source : Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.6.1	Summary of Actual and Change from Baseline in pre-dose morning FEV_1 (L) at Week 4, 8 and 12–- Main Estimand (Intenrion-To-Treat Set)	TPT001	- Descriptive statistics will be presented to summarize actual value and change from baseline at visit 3 (Week 4), visit 4 (Week 8) and visit 5 (Week 12) by treatment group for pre-dose morning FEV_1 (L). - Descriptive statistics will include n, Mean (SD), 95% CI for Mean, Median, Minimum, Maximum. - Data to be considered: include on-treatment and off-treatment data, but not imputed data.	Source: Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] Baseline is defined as the arithmetic mean of the pre-dose FEV_1 measurements (at 45 mins and 15 mins pre-dose) collected at week 0 (Visit 2). [2] No imputed data displayed.
Table 14.2.6.2	Statistical Analysis of Change from Baseline in pre-dose morning FEV_1 (L) at Week 4, 8 and 12–- Main Estimand (Intention-To-Treat Set)	ANT001	- ANCOVA model at visit 3 (Week 4), visit 4 (Week 8) and visit 5 (Week 12) including covariates as detailed in section 7.4 will be performed - Data to be considered: This statistical analysis will include on-treatment, off-treatment and imputed data. Missing data will be imputed using available off-treatment data (or a CR imputation) as detailed in section 7.3.1.	Source : Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).

Table 14.2.7.1	Summary of Actual and Change from Baseline in Average Morning PEF (L/min)over 12-weeks Treatment Period (Intention-to-Treat Set)	TPT001	- Descriptive statistics will be presented to summarize actual value and change from baseline for each inter-visit period (i.e., [Week 0– Week 4]; [Week 4 – Week 8] and [Week 8 – Week 12]) and over 12-week treatment period by treatment group for Average pre-dose Morning PEF (L/min) - Descriptive statistics include n, Mean (SD), 95% CI for Mean, Median, Minimum, Maximum. - Data to be considered: This descriptive summary will include on-treatment and off-treatment data, but not imputed data. Derive and summarize the parameter according to the definition provided at column "Definition for descriptive analysis" of the table reported in section 9.2.2.5.	Source: Listings 16.2.6.4 Footnotes: [1] Baseline pre-dose morning PEF calculated as the arithmetic mean of all derived morning "Best PEF" values from the morning eDiary session of the day after Visit 1 to the morning eDiary session of the day of Visit 2 (inclusive).[2] Average pre-dose morning PEF at each inter-visit period is defined as the arithmetic mean of all the available pre-dose morning best PEF values recorded in each inter-visit period. Average pre-dose morning PEF over the entire treatment period calculated as the arithmetic mean of the valid pre-dose morning Best PEF recorded from the morning session of the day after the first randomized study medication intake to the last morning session recorded in the treatment period. [3] The availability of at least 7 valid Best PEF is required for baseline period. The availability of at least 7 valid morning sessions per each inter-visit period are required to make the inter-visit period evaluable. The availability of at least 1 evaluable inter-visit period (at least 7 valid best PEF) is required for the entire treatment period. [4] Valid pre-dose Best PEF = Highest value from at least 2 PEF pre-dose measurements in the session in the range [50-900 L/min]. [5] The PEF sessions performed after the study medication intake are included in the analysis. [6] No imputed data displayed.
Table 14.2.7.2	Statistical Analysis of Change from Baseline in in average	ANT001	- ANCOVA model for each inter-visit period (i.e., [Week 0– Week 4]; [Week 4 – Week 8] and	Source: Listings 16.2.6.4

	Morning PEF (L/min) over 12-weeks Treatment Period(Intention-to-Treat Set)		[Week 8 – Week 12]) and over 12-week treatment period including covariates as detailed in section 7.4 will be performed. - Data to be considered: This statistical analysis will include on-treatment, off-treatment and imputed data. Missing data will be imputed using available off-treatment data (or a CR imputation) as detailed in section 7.3.1. Derive and summarize the parameter according to the definition provided at column "Definition for inferential analysis" of the table reported in section 9.2.2.5.	Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value as covariate. [2] Baseline pre-dose morning PEF calculated as the arithmetic mean of all derived morning "Best PEF" values from the morning eDiary session of the day after Visit 1 to the morning eDiary session of the day of Visit 2 (inclusive). [3] Average pre-dose morning PEF at each inter-visit period is defined as the arithmetic mean of all the available pre-dose morning best PEF values recorded in each inter-visit period. Average pre-dose morning PEF over entire treatment period is defined as the arithmetic mean of the three observed/imputed averages pre-dose morning PEF at inter-visit periods.. [4] The availability of at least 7 valid Best PEF is required for baseline period. The availability of at least 7 valid morning sessions per each inter-visit period are required to make the inter-visit period evaluable. Missing average-pre dose morning PEF at inter-visit period are imputed for each subject discontinuing from the study, according to the strategy defined in section 7.3.1, in order to obtain one observed/imputed average-pre dose morning PEF per each of the three inter-visit periods. [5] Valid pre-dose Best PEF = Highest value from at least 2 PEF pre-dose measurements in the session in the range [50-900 L/min]. [6] The PEF sessions performed after the study medication intake are included in the analysis.

Table 14.2.8.1	Summary of Actual and Change from Baseline in Average Evening PEF(L/min) over 12-week Treatment Period (Intention-to-Treat Set)	TPT001	- Descriptive statistics will be presented to summarize actual value and change from baseline for each inter-visit period (i.e., [Week 0– Week 4]; [Week 4 – Week 8] and [Week 8 – Week 12]) and over 12-week treatment period by treatment group for: Average pre-dose Evening PEF (L/min) - Descriptive statistics include n, Mean (SD), 95%CI for Mean, Median, Minimum, Maximum. - Data to be considered: This descriptive summary will include on-treatment and off-treatment data, but not imputed data. Derive and summarize the parameter according to the definition provided at column “Definition for descriptive analysis” of the table reported in section 9.2.2.6.	Source: Listing 16.2.6.4 Footnotes: [1] Baseline pre-dose evening PEF calculated as the arithmetic mean of all derived evening “Best PEF” values from the evening eDiary session of the day of Visit 1 to the evening eDiary session of the day before Visit 2 (inclusive). [2] Average pre-dose evening PEF at each inter-visit period calculated as the mean of all valid pre-dose evening Best PEF values recorded in each inter-visit period. Average pre-dose evening PEF over the entire treatment period calculated as the arithmetic mean of the valid pre-dose evening Best PEF values recorded from the evening session of the date of start of randomized treatment period to the evening session of the day of end of efficacy assessment period/ discontinuation. [3] The availability of at least 7 valid Best PEF is required for baseline period. The availability of at least 7 valid evening sessions per each inter-visit period are required to make the inter-visit period evaluable. The availability of at least 1 evaluable inter-visit period (7 valid Best PEF) is required for the entire treatment period. [4] Valid Best PEF = Highest value from at least 2 PEF pre-dose measurements in the session in the range [50-900 L/min]. [5] The PEF sessions performed after the study medication intake are included in the analysis. [6] No imputed data displayed.

Table 14.2.8.2	Statistical Analysis of Change from Baseline in in average Evening PEF (L/min) over 12-weeks Treatment Period (Intention-to-Treat Set)	ANT001	- ANCOVA model for each inter-visit period (i.e., [Week 0– Week 4]; [Week 4 – Week 8] and [Week 8 – Week 12]) and over 12-week treatment period including covariates as detailed in section 7.4 will be performed. - Data to be considered: This statistical analysis will include on-treatment, off-treatment and imputed data. Missing data will be imputed using available off-treatment data (or a CR imputation) as detailed in section 7.3.1. Derive and summarize the parameter according to the definition provided at column "Definition for inferential analysis" of the table reported in section 9.2.2.6.	Source: Listing 16.2.6.4 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value as covariate. [2] Baseline pre-dose evening PEF calculated as the arithmetic mean of all derived evening "Best PEF" values from the evening eDiary session of the day of Visit 1 to the evening eDiary session of the day before Visit 2 (inclusive). [3] Average pre-dose evening PEF at each inter-visit period is defined as the arithmetic mean of all the available pre-dose evening best PEF values recorded in each inter-visit period. Average pre-dose evening PEF over entire treatment period is defined as the arithmetic mean of the three observed/imputed averages pre-dose evening PEF at inter-visit periods. [4] The availability of at least 7 valid Best PEF is required for baseline period. The availability of at least 7 valid evening sessions per each inter-visit period are required to make the inter-visit period evaluable. Missing average-pre dose evening PEF at inter-visit period are imputed for each subject discontinuing from the study, according to the strategy defined in SAP section 7.3.1, in order to obtain one observed/imputed average-pre dose evening PEF per each of the three inter-visit periods. [5] Valid Best PEF = Highest value from at least 2 PEF pre-dose measurements in the session in the range [50-900 L/min].

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
				[6] The PEF sessions performed after the study medication intake are included in the analysis.
Table 14.2.9.1	Summary Statistics of pre-dose Morning FEV_1 Responders at Week 4, 8 and 12 (Intention-To-Treat Set)	TPT005	- Descriptive statistics will be presented to summarize for visit 3 (Week 4), visit 4 (Week 8) and visit 5 (Week 12) by treatment group for pre-dose Morning FEV_1 Responders - Descriptive statistics include number (r) and percentage of responders. - Display for column per each treatment arm the number (n) of participant in each visit (the denominator for percentage) - Data to be considered: include on-treatment and off-treatment data, but not imputed data.	Source: Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] Baseline is defined as the arithmetic mean of the pre-dose FEV_1 measurements (at 45 mins and 15 mins pre-dose) collected at week 0 (Visit 2). [2] A subject is defined as a responder if the change from baseline in pre-dose morning $FEV_1 \geq 100$ mL. [3] No imputed data displayed. [4] Percentage is derived as the number of responders (r) divided the number of non-missing observations (n) on each visit.
Table 14.2.9.2	Statistical Analysis of pre-dosed morning FEV_1 Responders at Week 4, 8 and 12 (Intention-To-Treat Set)	ANT003	- Logistic regression model at visit 3 (Week 4), visit 4 (Week 8) and visit 5 (Week 12) including covariates as detailed in section 7.4 will be performed. - Data to be considered: This statistical analysis will include on-treatment, off-treatment and imputed data. Missing data will be imputed using available off-treatment data (or a CR imputation) as detailed in section 7.3.1.	Source : Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] Logistic regression model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation). [3] A subject is defined as a responder if the change from baseline in pre-dose morning $FEV_1 \geq 100$ mL.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.10.1	Summary Statistics of trough FEV_1 responders (Intention-To-Treat Set)	TPT005	- Descriptive statistics will be presented to summarize for visit 2 (Week 0, Day1) and visit 5 (Week 12) by treatment group for: Trough FEV_1 Responders - Descriptive statistics include number (r) and percentage of responders. - Display for column per each treatment arm the number (n) of participant in each visit (the denominator for percentage) - Data to be considered: include on-treatment and off-treatment data, but not imputed data.	Source: Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] Baseline is defined as the arithmetic mean of the pre-dose FEV_1 measurements (at 45 mins and 15 mins pre-dose) collected at week 0 (Visit 2). [2] A subject is defined as a responder if the change from baseline in through $FEV_1 \geq 100$ mL. [3] No imputed data displayed. [4] Percentage is based on the number of responders (r) divided the number of non-missing observations (n) on each visit.
Table 14.2.10.2	Statistical Analysis of trough FEV_1 responders at Week 12 (Intention-To-Treat Set)	ANT003	- Logistic regression model at visit 2 (Week 0, Day1) and visit 5 (Week 12) including covariates as detailed in section 7.4 will be performed. - Data to be considered: This statistical analysis will include on-treatment, off-treatment and imputed data. Missing data will be imputed using available off-treatment data (or a CR imputation) as detailed in section 7.3.1.	Source : Listings 16.2.6.1.1 to 16.2.6.1.4 Footnotes: [1] Logistic regression model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation). [3] A subject is defined as a responder if the change from baseline in trough $FEV_1 \geq 100$ mL.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.11.1	Summary of Actual and Change from Baseline in ACQ-5 and ACQ-7 Score (Intention-To-Treat Set)	TPT001	- Descriptive statistics will be presented to summarize actual value and change from baseline at visit 3 (Week 4), visit 4 (Week 8) and visit 5 (Week 12) by treatment group for ACQ-5 Score and ACQ-7 Score. - Descriptive statistics will include n, Mean (SD), 95% CI for Mean, Median, Minimum, Maximum. - Data to be considered: include on-treatment and off-treatment data, but not imputed data.	Source: Listing 16.2.6.7 Footnotes: [1] ACQ-5/7 = Asthma Control Questionnaire-5/7 items. [2] Baseline value is defined as the ACQ-5/7 score collected at Week 0. [3] No imputed data displayed.
Table 14.2.11.2	Statistical Analysis of Change from Baseline in ACQ-7 Score at Week 12 (Intention-To-Treat Set)	ANT001	- ANCOVA model at visit 3 (Week 4), visit 4 (Week 8) and visit 5 (Week 12) including covariates as detailed in section 7.4 will be performed. - Data to be considered: This statistical analysis will include on-treatment, off-treatment and imputed data. Missing data will be imputed using available off-treatment data (or a CR imputation) as detailed in section 7.3.1.	Source: Listing 16.2.6.7 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0) as covariate. [2] Baseline value is defined as the ACQ-7 score collected at Week 0. [3] Missing data are imputed using available off-treatment data (or a CR imputation).
Table 14.2.11.3	Statistical Analysis of Change from Baseline in ACQ-5 Score at Week 12 (Intention-To-Treat Set)	ANT001	- ANCOVA model at visit 3 (Week 4), visit 4 (Week 8) and visit 5 (Week 12) including covariates as detailed in section 7.4 will be performed. - Data to be considered: This statistical analysis will include on-treatment, off-treatment and imputed data. Missing data will be imputed using available off-treatment data (or a CR imputation) as detailed in section 7.3.1.	Source: Listing 16.2.6.7 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0) as covariate. [2] Baseline value is defined as the ACQ-5 score collected at Week 0. [3] Missing data are imputed using available off-treatment data (or a CR imputation).

Table 14.2.12.1	Summary of Actual and Change from Baseline in Percentage of Rescue Medication-free Days over 12-week Treatment Period(Intention-to-Treat Set)	TPT001	- Descriptive statistics will be presented to summarize actual value and change from baseline for all inter-visit periods (i.e., [Week 0– Week 4]; [Week 4 – Week 8] and [Week 8 – Week 12]) and over 12-week treatment period by treatment group for Percentage of Rescue Medication-free Days. - Descriptive statistics will include n, Mean (SD), 95% CI for Mean, Median, Minimum, Maximum. - Data to be considered: include on-treatment and off-treatment data, but not imputed data. Derive and summarize the parameter according to the definition provided at column “Definition for descriptive analysis” of the table reported in section 9.2.2.10.	Source: Listing 16.2.6.5 Footnotes: [1] A rescue medication-free day is a day with daily use of rescue medication = 0. For each day, the rescue medication free-day will be calculated only if data of day-time intake (recorded at evening session) and night-time intake (recorded at morning sessions of the next day) are available. [2] Baseline Percentage of rescue medication-free days calculated as the percentage of days with no rescue medication collected during the run-in period. [3] Percentage of rescue medication-free days at each inter-visit period defined as the ratio of the number of days with no rescue medication during the inter-visit period and the number of days on which daily rescue medication use is assessed the inter-visit period. Percentage of rescue medication-free days over the entire treatment period defined as the ratio of number of days with no rescue medication over entire treatment period and the number of days on which daily rescue medication use is assessed over entire treatment period. [4] The availability of at least 7 valid diary entries is required for baseline period. The availability of at least 7 valid days per each inter-visit period is required to make the inter-visit period evaluable. The availability of at least 1 evaluable inter-visit period is required over all treatment period to make the entire treatment period evaluable. [5] No imputed data displayed

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.2.12.2	Statistical Analysis of Change from Baseline in Percentage of Rescue Medication-free Daysover 12-week Treatment Period (Intention-to-Treat Set)	ANT001	- ANCOVA model at all inter-visit periods (i.e., [Week 0– Week 4]; [Week 4 – Week 8] and [Week 8 – Week 12]) and over 12-week treatment period including covariates as detailed in section 7.4 will be performed. - Data to be considered: This statistical analysis will include on-treatment, off-treatment and imputed data. Missing data will be imputed using available off-treatment data (or a CR imputation) as detailed in section 7.3.1. Derive and summarize the parameter according to the definition provided at column "Definition for inferential analysis" of the table reported in Section 9.2.2.10.	Source: Listing 16.2.6.5 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value as covariate. [2] A rescue medication-free day is a day with daily use of rescue medication = 0. For each day, the rescue medication free-day will be calculated only if data of day-time intake (recorded at evening session) and night-time intake (recorded at morning sessions of the next day) are available. [3] Baseline Percentage of rescue medication-free days calculated as the percentage of days with no rescue medication collected during the run-in period. [4] Percentage of rescue medication-free days at each inter-visit period defined as the ratio of the number of days with no rescue medication during the inter-visit period and the number of days on which daily rescue medication use is assessed during the inter-visit period. Percentage of rescue medication-free days over the entire treatment period defined as the arithmetic mean of the three observed/imputed percentages of rescue medication-free days at inter-visit periods. [5] The availability of at least 7 valid diary entries is required for baseline period. [6] Missing data are imputed using available off-treatment data (or a CR imputation).

Table 14.2.13.1	Summary of Actual and Change from Baseline in Percentage of Asthma Symptom-free days over 12-week Treatment Period (Intention-to-Treat Set)	TPT001	- Descriptive statistics will be presented to summarize actual value and change from baseline for all inter-visit periods (i.e., [Week 0– Week 4]; [Week 4 – Week 8] and [Week 8 – Week 12]) and over 12-week treatment period by treatment group for Percentage of Asthma Symptom-free Days. - Descriptive statistics will include n, Mean (SD), 95% CI for Mean, Median, Minimum, Maximum. - Data to be considered: include on-treatment and off-treatment data, but not imputed data. Derive and summarize the parameter according to the definition provided at column "Definition for descriptive analysis" of the table reported in section 9.2.2.11.	Source: Listing 16.2.6.6 Footnotes: [1] An asthma symptom-free day is a day with total daily asthma symptom score = 0. For each day, the asthma symptom-free day will be calculated only if data of day-time intake (recorded at evening session) and night-time intake (recorded at morning sessions of the next day) are available. [2] Baseline Percentage of asthma symptom-free days calculated as the percentage of days with no asthma symptom collected during the run-in period. [3] Percentage of asthma symptom-free days at each inter-visit period defined as the ratio of the number of days with no asthma symptom during the inter-visit period and the number of days with available daily record of asthma symptom during the inter-visit period. Percentage of asthma symptom-free days over the entire treatment period defined as the ratio of number of days with no asthma symptom over entire treatment period and the number of days with available daily record of asthma symptom over entire treatment period. [4] The availability of at least 7 valid diary entries is required for baseline period. The availability of at least 7 valid days per each inter-visit period is required to make the inter-visit period evaluable. The availability of at least 1 evaluable inter-visit period is required over all treatment period to make the entire treatment period evaluable. [5] No imputed data displayed
Table 14.2.13.2	Statistical Analysis of Change from Baseline in Percentage of	ANT001	- ANCOVA model at all inter-visit periods (i.e., [Week 0– Week 4]; [Week 4 – Week 8] and	Source: Listing 16.2.6.6

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
	Asthma Symptom-free Days over 12-week Treatment Period (Intention-to-Treat Set–- Subset)		[Week 8 – Week 12]) and over 12-week treatment period including covariates as detailed in section 7.4 will be performed. - Data to be considered: This statistical analysis will include on-treatment, off-treatment and imputed data. Missing data will be imputed using available off-treatment data (or a CR imputation) as detailed in section 7.3.1. Derive and summarize the parameter according to the definition provided at column "Definition for inferential analysis" of the table reported in section 9.2.2.11.	Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value as covariate. [2] An asthma symptom-free day is a day with total daily asthma symptom score = 0. For each day, the asthma symptom-free day will be calculated only if data of day-time intake (recorded at evening session) and night-time intake (recorded at morning sessions of the next day) are available. [3] Baseline percentage of asthma symptom-free days calculated as the percentage of days with no asthma symptom collected during the run-in period. [4] Percentage of asthma symptom-free days at each inter-visit period defined as the ratio of the number of days with no asthma symptom during the inter-visit period and the number of days with available daily record of asthma symptom during the inter-visit period. Percentage of asthma symptom-free days over the entire treatment period defined as the arithmetic mean of the three observed/imputed percentages of rescue medication-free days at inter-visit periods. [5] The availability of at least 7 valid diary entries is required for baseline period. [6] Missing data are imputed using available off-treatment data (or a CR imputation).

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.1	Study Treatment Exposure (Safety Set)	EXT001	Include summary statistics for Exposure (weeks) and Exposure categories (weeks) [0-4), [4-8), [8, 12- (ETD)].	Source: Listing 16.2.5.3 Footnote: [1] Extent of exposure (weeks) = (Date of last randomized study medication intake–- date of first randomized study medication intake + 1) / 7. [2] ETD = Early Treatment Discontinuation

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.2.1	Summary of Treatment Emergent Adverse Events (Safety Set)	AET001	- Do not display Overall column. - Filter only for treatment emergent adverse events. - Display for column per each treatment arm (i.e., number and percentage of subjects having at least one event, total number of events and incidence density): #1 n, #2 (%). #3 E #4 I - Include rows for Number of Subjects with at Least One: - TEAEs [1] - Drug related TEAEs (ADRs) [2] - Serious TEAEs [3] - Non-serious TEAEs [4] - Serious ADRs [5] - Severe TEAEs [6] - TEAEs Leading to Study Drug Discontinuation [7] - TEAEs Leading to Death [8] - Diagnosis of COVID-19	Source: Listings 16.2.7.2 to 16.2.7.9. Footnotes: [1] Adverse events starting on or after the first study drug intake and up to 1 week after the last dose of study drug intake are classified as treatment emergent adverse even (TEAE). [2] An ADR is an AE judged as related to the study medication. In case of missing relationship, the event is considered related. [3] A Serious AE (SAE) is an AE judged as serious. [4] A non-serious AE is an AE judged as non-serious. [5] A serious ADR is a SAE judged as having a reasonable possibility of relatedness to the study medication. In case of missing relationship, the event is considered related. [6] A severe AE is an AE with severe intensity. In case of missing severity, AE is considered severe. [7] An AE leading to study drug discontinuation is an AE with action taken with study drug equal to 'Drug permanently withdrawn'. [8] An AE leading to death is an AE with outcome equal to 'Fatal'. [9] The incidence density (I) is estimated as the number of subjects with at least one event divided by the total person-years of exposure to study drug multiplied by 100 (events per 100 person-years).

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.2.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003	- Do not display Overall column. - Filter only for treatment emergent adverse events. - Display for column per each treatment arm (i.e., number and percentage of subjects having at least one event, total number of events and incidence density): #1 n, #2 (%). #3 E #4 I - Display by System Organ Class (SOC) and by Preferred Term (PT) sorted by alphabetical order.	Source: Listing 16.2.7.2. Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by SOC and PT. [3] The incidence density (I) is estimated as the number of subjects with at least one event divided by the total person-years of exposure to study drug multiplied by 100 (events per 100 person-years).
Table 14.3.2.3	Adverse Drug Reactions by System Organ Class and Preferred Term (Safety Set)	AET003	Same as Table 14.3.2.2.	Source: Listing 16.2.7.5 Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by SOC and PT. [3] The incidence density (I) is estimated as the number of subjects with at least one event divided by the total person-years of exposure to study drug multiplied by 100 (events per 100 person-years).

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.2.4	Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003	Same as Table 14.3.2.2.	Source: Listing 16.2.7.3 Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by SOC and PT. [3] The incidence density (I) is estimated as the number of subjects with at least one event divided by the total person-years of exposure to study drug multiplied by 100 (events per 100 person-years).
Table 14.3.2.5	Non-Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003	Same as Table 14.3.2.2.	Source: Listing 16.2.7.4 Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by SOC and PT. [3] The incidence density (I) is estimated as the number of subjects with at least one event divided by the total person-years of exposure to study drug multiplied by 100 (events per 100 person-years).

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.2.6	Serious Adverse Drug Reactions by System Organ Class and Preferred Term (Safety Set)	AET003	Same as Table 14.3.2.2.	Source: Listing 16.2.7.6 Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by SOC and PT. [3] The incidence density (I) is estimated as the number of subjects with at least one event divided by the total person-years of exposure to study drug multiplied by 100 (events per 100 person-years).
Table 14.3.2.7	Severe Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)	AET003	Same as Table 14.3.2.2.	Source: Listing 16.2.7.7 Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by SOC and PT. [3] The incidence density (I) is estimated as the number of subjects with at least one event divided by the total person-years of exposure to study drug multiplied by 100 (events per 100 person-years).

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.2.8	Treatment Emergent Adverse Events Leading to Discontinuation from Study Drug by System Organ Class and Preferred Term (Safety Set)	AET003	Same as Table 14.3.2.2.	Source: Listing 16.2.7.8 Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by SOC and PT. [3] The incidence density (I) is estimated as the number of subjects with at least one event divided by the total person-years of exposure to study drug multiplied by 100 (events per 100 person-years).
Table 14.3.2.9	Treatment Emergent Adverse Events leading to Death by System Organ Class and Preferred Term (Safety Set)	AET003	Same as Table 14.3.2.2.	Source: Listing 16.2.7.9 Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by SOC and PT.

Table 14.3.2.10	Statistical Analysis of TEAEs (Safety Set)	Not available	Display as a sub header: - Number of subjects with at least one: Present for each the following categories: TEAE, ADR, SAE, SADR, Severe AE, AE Leading to Treatment Discontinuation, AE Leading to Death the Risk Difference along with 95%CI. Analysis to be made only if only the event occurred in at least 5 subjects.	Source: Listings 16.2.7.2 to 16.2.7.9. Footnotes: [1] Adverse events starting on or after the first study drug intake and up to 1 week after the last dose of study drug intake are classified as treatment emergent adverse even (TEAE). [2] An ADR is an AE judged as having a reasonable possibility of relatedness to the study medication. In case of missing relationship, the event is considered related. [3] A Serious AE (SAE) is an AE judged as serious. [4] A serious ADR is a SAE judged as having a reasonable possibility of relatedness to the study medication. In case of missing relationship, the event is considered related. [5] A severe AE is an AE with severe intensity. In case of missing severity, AE is considered severe. [6] An AE leading to study drug discontinuation is an AE with action taken with study drug equal to 'Drug permanently withdrawn'. [7] An AE leading to death is an AE with outcome equal to 'Fatal'. [8] The risk difference is calculated considering the crude proportion of subjects with the selected event in the two treatment groups (i.e., number of subjects of the treatment group with the selected event / number of subjects of the treatment group). [9] The 95% CIs for the risk difference is calculated using the Newcombe Hybrid Score method.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
				[10] The comparative analysis (i.e., estimation of risk difference and its 95% CI) will not be carried out if the total number of subjects with the event in the overall Safety Set is < 5.
Table 14.3.2.11	Statistical Analysis of TEAEs by SOC and PT (Safety Set)	Not available	Display as a sub header: - Number of subjects with at least one: Present for each the following categories: TEAE by SOC, TEAE by PT, SAE by SOC, SAE by PT, the risk difference along with 95%CI. Analysis to be made only if only the event occurred in at least 5 subjects.	Source: Listings 16.2.7.2 to 16.2.7.9. Footnotes: [1] AEs are coded using the MedDRA dictionary (version XX.X). [2] The risk difference is calculated considering the crude proportion of subjects with the selected event in the two treatment groups (i.e., number of subjects of the treatment group with the selected event / number of subjects of the treatment group). [3] The 95% CIs for the risk difference is calculated using the Newcombe Hybrid Score method. [4] The comparative analysis (i.e., estimation of risk difference and its 95% CI) will not be carried out if the total number of subjects with the event in the overall Safety Set is < 5.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.2.12	Summary of Class-Related Treatment Emergent Adverse Events (Safety Set)	AET001	- Do not display Overall column. - Filter only for class-related treatment emergent adverse events. - Display for column per each treatment arm (i.e., number and percentage of subjects having at least one event, total number of events and incidence density): #1 n, #2 (%). #3 E #4 I - Include rows for Number of Subjects with at Least One: - TEAE [1] - Drug related TEAE (ADR) [2] - Serious TEAE [3] - Non-serious TEAE [4] - Serious ADR [5] - Severe TEAEs [6] - TEAE Leading to Study Drug Discontinuation [7] - TEAE Leading to Death [8] - Diagnosis of COVID-19	Source: Listing 16.2.7.10. Footnotes: [1] Adverse events starting on or after the first study drug intake and up to 1 week after the last dose of study drug intake are classified as treatment emergent adverse even (TEAE). [2] An ADR is an AE judged as having a reasonable possibility of relatedness to the study medication. In case of missing relationship, the event is considered related. [3] A Serious AE (SAE) is an AE judged as serious. [4] A non-serious AE is an AE judged as non-serious. [5] A serious ADR is a SAE judged as having a reasonable possibility of relatedness to the study medication. In case of missing relationship, the event is considered related. [6] A severe AE is an AE with severe intensity. In case of missing severity, AE is considered severe. [7] An AE leading to study drug discontinuation is an AE with action taken with study drug equal to 'Drug permanently withdrawn'. [8] An AE leading to death is an AE with outcome equal to 'Fatal'. [9] The incidence density (I) is estimated as (the number of subjects with at least one event divided by the total person-years of exposure to study drug)*100.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.2.13	Class-Related Treatment Emergent Adverse Events by Medical Concept (Safety Set)	AET003	- Do not display Overall column. - Filter only for class-related treatment emergent adverse events. - Display for column per each treatment arm (i.e., number and percentage of subjects having at least one event, total number of events and incidence density): #1 n, #2 (%). #3 E #4 I - Display by Medical Concept 1 and Medical Concept 2 according to the list shown in section 10.2.2.	Source: Listing 16.2.7.10. Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by medical concepts. [3] The incidence density (I) is estimated as the number of subjects with at least one event divided by the total person-years of exposure to study drug multiplied by 100 (events per 100 person-years).
Table 14.3.2.14	Class-Related Adverse Drug Reactions by Medical Concept (Safety Set)	AET003	Same as Table 14.3.2.13.	Source: Listing 16.2.7.10. Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by medical concepts.
Table 14.3.2.15	Class-Related Serious Treatment Emergent Adverse Events by Medical Concepts (Safety Set)	AET003	Same as Table 14.3.2.13.	Source: Listing 16.2.7.10. Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by medical concepts.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.2.16	Class-Related Non-Serious Treatment Emergent Adverse Events by Medical Concept (Safety Set)	AET003	Same as Table 14.3.2.13.	Source: Listing 16.2.7.10. Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by medical concepts.
Table 14.3.2.17	Class-Related Serious Adverse Drug Reactions by Medical Concept (Safety Set)	AET003	Same as Table 14.3.2.13.	Source: Listing 16.2.7.10. Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by medical concepts.
Table 14.3.2.18	Class-Related Severe Treatment Emergent Adverse Events by Medical Concept (Safety Set)	AET003	Same as Table 14.3.2.13.	Source: Listing 16.2.7.10. Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by medical concept.
Table 14.3.2.19	Class-Related Treatment Emergent Adverse Events Leading to Discontinuation from Study Drug by Medical Concept (Safety Set)	AET003	Same as Table 14.3.2.13.	Source: Listing 16.2.7.10. Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by medical concept.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.2.20	Class-Related Treatment Emergent Adverse Events leading to Death by Medical Concept (Safety Set)	AET003	Same as Table 14.3.2.13.	Source: Listing 16.2.7.10. Footnotes: [1] TEAEs are coded using the MedDRA dictionary (version XX.X). [2] Multiple occurrences of the same event within a subject are counted once in the summaries by medical concept.

Table 14.3.2.21	Statistical Analysis of Class-Related TEAEs (Safety Set)	Not available	- Filter only for class-related treatment emergent adverse events. Display as a sub header: - Number of subjects with at least one: Present for each the following categories: TEAE, ADR, SAE, SADR, Severe AE, AE Leading to Treatment Discontinuation, AE Leading to Death the Risk Difference along with 95%CI. Analysis to be made only if only the event occurred in at least 5 subjects.	Source: Listing 16.2.7.10. Footnotes: [1] Adverse events starting on or after the first study drug intake and up to 1 week after the last dose of study drug intake are classified as treatment emergent adverse even (TEAE). [2] An ADR is an AE judged as having a reasonable possibility of relatedness to the study medication. In case of missing relationship, the event is considered related. [3] A Serious AE (SAE) is an AE judged as serious. [4] A serious ADR is a SAE judged as having a reasonable possibility of relatedness to the study medication. In case of missing relationship, the event is considered related. [5] A severe AE is an AE with severe intensity. In case of missing severity, AE is considered severe. [6] An AE leading to study drug discontinuation is an AE with action taken with study drug equal to 'Drug permanently withdrawn'. [7] An AE leading to death is an AE with outcome equal to 'Fatal'. [8] The risk difference is calculated considering the crude proportion of subjects with the selected event in the two treatment groups (i.e., number of subjects of the treatment group with the selected event / number of subjects of the treatment group). [9] The 95% CIs for the risk difference is calculated using the Newcombe Hybrid Score method.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
				[10] The comparative analysis (i.e., estimation of risk difference and its 95% CI) will not be carried out if the total number of subjects with the event in the overall Safety Set is < 5.
Table 14.3.2.22	Statistical Analysis of Class-Related TEAEs by Medical Concept (Safety Set)	Not available	- Filter only for class-related treatment emergent adverse events. Display as a sub header: - Number of subjects with at least one: Present for each the following categories: TEAE by SOC, TEAE by PT, SAE by SOC, SAE by PT, the risk difference along with 95%CI. Analysis to be made only if only the event occurred in at least 5 subjects.	Source: Listing 16.2.7.10. Footnotes: [1] AEs are coded using the MedDRA dictionary (version XX.X). [2] The risk difference is calculated considering the crude proportion of subjects with the selected event in the two treatment groups (i.e., number of subjects of the treatment group with the selected event / number of subjects of the treatment group). [3] The 95% CIs for the risk difference is calculated using the Newcombe Hybrid Score method. [4] The comparative analysis (i.e., estimation of risk difference and its 95% CI) will not be carried out if the total number of subjects with the event in the overall Safety Set is < 5.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.3.1	Vital Signs: Summary of Actual Values and Change from Baseline (Safety Set)	VST001	- Include parameters Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Pulse Rate (beats/min), Body weight (kg). - For SBP and DPB, summary statistics at: - Visit 2 (Week 0): pre-dose (baseline), 30 min, 1, 4 and 12h post-dose; -Visit 3 (Week 4) & Visit 4 (Week 8): pre-dose; - Visit 5 – Week 12: pre-dose, 30 min, 1, 4 and 12h post-dose. - For body weight, summary statistics at: - Visit 2 (Week 0): pre-dose (baseline); - Visit 5 (Week 12): pre-dose. - Display n, Mean, SD, 95% CI for the Mean, Median, Minimum and Maximum.	Source: Listing 16.2.8.1 Footnote: [1] Baseline value is defined as the pre-dose value collected at Visit 2 (Week 0, Day1).
Table 14.3.4.1	ECG Results: Actual Values and Change from Baseline and Pre-dose (Safety Set)	EGT002	- Present descriptive statistics for HR, QTcF, QRS and PR at pre-dose and 30 min, 1, 4 and 12-hours post-dose of each scheduled visit [i.e., visit 2 (Week 0) & visit 5 (Week 12): serial; visit 3 (Week 4) & visit 4 (Week 8): pre-dose only]. Descriptive statistics will include n, Mean (SD), 95% CI for Mean, Median, Minimum, Maximum. - Present change from baseline to each pre-dose [at visit 3 (Week 4), visit 4 (Week 8) and visit 5 (Week 12)]and change from pre-dose at visit to each post-dose value (i.e., 30 mins, 1, 4 and 12h) of the same visit for visit 2 (W0) and visit 5 (W12) only. Descriptive statistics will include n, Mean (SD), 90% CI for Mean difference, Median, Minimum, Maximum.	Source: Listing 16.2.9.1 [1] Baseline value is defined as the pre-dose value collected at Visit 2 (Week 0, Day1).

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.4.2	QTcF Abnormalities (Safety Set)	EGT007	- Present the summary "At Any Post-baseline Timepoint" and then at "each timepoint", including the serial assessments when applicable: - Visit 2 – Week 0:30 min, 1, 4 and 12h post-dose; -Visit 3 – Week 4: pre-dose - Visit 4 – Week 8: pre-dose; - Visit 5 – Week 12: pre-dose, 30 min, 1, 4 and 12h post-dose.- Replace 'At Any Timepoint' by 'At Any Post-baseline Timepoint [1]'. Present the abnormalities as follow: QTcF >450 ms, >480 ms and >500 ms for males and QTcF >470 ms and >500 ms for females- All categories listed have to be reported, even if empty ('0' count).	Source: Listing 16.2.9.2 Footnote: [1] A subject can be counted in several categories.
Table 14.3.4.3	QTcF Abnormal Changes – Change from Baseline to Pre-dose (Safety Set)	EGT008	- Present the summary of change from baseline to pre-dose "At Any Post-baseline Timepoint" and then at "each timepoint" [i.e., visit 3 (W4), visit 4 (W8) and visit 5 (W12)]. - Replace 'At Any Timepoint' by 'At Any Post-baseline Timepoint [1]'. Display the following Abnormalities: Pre-dose QTcF increase from baseline >30 ms Pre-dose QTcF increase from baseline >60 ms. - All categories listed have to be reported, even if empty ('0' count). - Remove 'timepoint' from the label 'Visit – Timepoint' since it will be always the same	Source: Listing 16.2.9.2 Footnotes: [1] A subject can be counted in several categories. [2] Baseline value is defined as the pre-dose value collected at Visit 2 (i.e., Week 0).

Table 14.3.4.4	QTcF Abnormal Changes – Change from Pre-dose to Post-dose (Safety Set)	EGT008	- Present the summary of change from pre-dose to post-dose “At Any Post-baseline Timepoint” and then at “each timepoint” [i.e., visit 2 (W0) and visit 5 (W12)]. - Replace ‘At Any Timepoint’ by ‘At Any Post-baseline Timepoint [1]’. - Display the following Abnormalities: Any post-dose QTcF increase from pre-dose >30 ms; Any post -dose QTcF increase from pre-dose >60 ms. 30 min post-dose QTcF increase from pre-dose >30 ms; 30 min post -dose QTcF increase from pre-dose >60 ms. 1 h post-dose QTcF increase from pre-dose >30 ms; 1 h post -dose QTcF increase from pre-dose >60 ms. 4 h post-dose QTcF increase from pre-dose >30 ms; 4 h post -dose QTcF increase from pre-dose >60 ms. 12 h post-dose QTcF increase from pre-dose >30 ms; 12 h post -dose QTcF increase from pre-dose >60 ms. - All categories listed have to be reported, even if empty (‘0’ count).	Source: Listing 16.2.9.2 Footnote: [1] A subject can be counted in several categories.

Table Number	Table Title	Template Code	Notes	Footnotes/Source Listing Number
Table 14.3.4.5	ECG: Overall Interpretation from Investigator (Safety Set)	EGT001	- Present for all scheduled visits (i.e., visit 2 W0, visit 3 W4, visit 4 W8 and visit 5 W12). - 'Subject with Pacemaker' to be deleted. - The interpretation is the one from Investigator (not from central reading).	Source: Listing 16.2.9.1
Table 14.3.5.1	Hematology: Summary of Actual Values and Change from Baseline (Safety Set)	LBT001	Present summary for actual at Week 0 and Week 12 and change from baseline at Week 12 in hematology parameters listed in section 10.5 of the SAP (sorted by alphabetic order).	Source: Listing 16.2.10.1 Footnote: [1] Baseline value is defined as the value collected at Visit 1 – Screening visit.
Table 14.3.5.2	Blood Chemistry: Summary of Actual Values and Change from Baseline (Safety Set)	LBT001	Present summary for actual at Week 0 and Week 12 and change from baseline at Week 12 in blood chemistry parameters listed in section 10.5 of the SAP (sort by alphabetic order).	Source: Listing 16.2.10.2 Footnote: [1] Baseline value is defined as the value collected at Visit 1 – Screening visit.
Table 14.3.5.3	Hematology: Shifts from Baseline to Week 12 (Safety Set)	LBT004	Present summary for parameters listed in section 10.5 of the SAP (sorted by alphabetic order).	Source: Listing 16.2.10.1 Footnote: [1] Baseline value is defined as the value collected at Visit 1 – Screening visit.
Table 14.3.5.4	Biochemistry Results: Shifts from Baseline to Week 12 (Safety Set)	LBT004	Present summary for parameters listed in section 10.5 of the SAP (sorted by alphabetic order).	Source: Listing 16.2.10.2 Footnote: [1] Baseline value is defined as the value collected at Visit 1 – Screening visit.

16.2 Listings

For each relevant listing, near the Subject ID, the following flags will be added:

COVID-19 diagnosed;

§ Vaccinated against COVID-19.

For each relevant listing, near the Visit name, the following flag will be added:

* Off-treatment visit;

° Remote visit. (if applicable).

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.1.7	Randomization Schedule (Randomized Set)	DSL001	- Add the info about stratification factors: Prior Asthma Therapy at Screening/Study Entry (3 levels – "Medium dose ICS/LABA" vs. "Medium dose ICS" vs. "High dose ICS") and US Region (4 levels – "Northeast" vs. "Midwest" vs. "South" vs. "West"	
Listing 16.2.1.1	Screening Failures (Enrolled Set)	DSL002	- Include only subjects who discontinued before the randomization.	
Listing 16.2.1.2	Subjects Disposition (Randomized Set)	DSL004	- 'Period of last intake of study treatment' and 'Last treatment received' columns not to be displayed. - Include Date of Last Dose. - Include Day [1], Day [2] and Day [3]. - Display the date and the reason of treatment termination before study termination column. - Add column 'Did the subject discontinue the treatment due to COVID-19?'	Footnotes: [Day 1] is the study Day at Date of Study Discontinuation calculated with reference to the Informed Consent Date. [Day 2] is the study Day at Date of Study Discontinuation calculated with reference to the First Dose Date. [Day 3] is the study Day at Date of Study Discontinuation calculated with reference to the Last Dose Date.
Listing 16.2.1.3	Randomization Code Broken (Randomized Set)	DSL005	- Only subject for which the code was broken are to be presented in this listing	

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.1.4	Study Visits (Randomized Set)	SVL001	- Remove the word 'Retest' in header. - Remove study day in period. - The follow-up call and ETD are considered as a visit. - Add column 'Visit not Done due to COVID-19?'	Footnotes: [1] * Off-treatment visit. [2] ° Remote visit. [3] The on-treatment period is defined as the period between the date of first randomized study medication intake and the date of last randomized study medication intake (extremes included). [4] The off-treatment period, in case subject accepts to attend post-treatment visits, is defined as the period between the day after the date of last randomized study medication intake and the date of study conclusion (extremes included). [5] ETD = Early Treatment Discontinuation
Listing 16.2.2.1	Important Protocol Deviation (Randomized Set)	DVL002	- Include all important deviations from DV. - Remove "Period" column. - Add visits column (2, 3, 4, 5) - Add timepoints column - In the column 'Category', display 'L' or 'NL'. - Replace 'Randomized Sequence' with 'Randomized Treatment'. Timepoints are: - Visit 2: -45 and -15 min pre-dose and 5, 15, 30 min, 1h, 2h, 3h, 6h, 9h, 11.5h and 12h post-dose - Visit 3: pre-dose - Visit 4: pre-dose - Visit 5: -45 and -15 min pre-dose and 5, 15, 30 min, 1h, 2h, 3h, 6h, 9h, 11.5h and 12h post-dose.	Footnote: [1] L = Leading to population exclusion; NL = Not leading to population exclusion.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.2.2	Violation of Eligibility Criteria (Randomized Set)	DVL001	- Only deviations from DV in relation to inclusion/exclusion criteria.	
Listing 16.2.3.1	Analysis Set Disposition (Randomized Set)	DSL006	- Display Randomized, ITTand Safety sets.	Footnotes: [1] The Randomized set includes all randomized subjects. [2] The Safety set includes all randomized subjects who received at least one dose of study treatment. [3] The Intention-to-Treat set includes all randomized subjects who received at least one dose of the study treatment.
Listing 16.2.3.2	Subjects Excluded from Analysis Sets (Randomized Set)	DSL007	- Present for Safety and ITT sets.	
Listing 16.2.4.1	Demographic Characteristics (Randomized Set)	DML001	- Include age, age group <65; >= 65), sex, race *(list all categories if several),* ethnicity, height, weight, BMI, and childbearing potential.	Footnote: [1] BMI calculated as: weight (kg) / height $(m)^2$

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.4.2	Smoking Status (Randomized Set)	SUL001	The following columns will be presented: - Subject ID - Randomized Treatment - Visit - Date - Smoking Status (Non-smoker, Ex-smoker, Smoker) - Smoking start / Stop date - Smoking Duration (years) - Number of Pack-years - Category (Tobacco products/eCigarettes) - Type (Tobacco products: Cigarettes/Cigars or spliffs/Cigarillos/Pipe, eCigarettes: Nicotine based, Not Nicotine based) - Average Number of Day - Total Number of Smoking Years Note: Replaces "SMOKING STATUS AT SCREENING/ CHANGE IN SMOKING STATUS" By "SMOKING STATUS"	Footnote: [1] For ex-smokers, duration of smoking (years) will be calculated as (stop date – start date + 1)/365.25.
Listing 16.2.4.3	Asthma History (Randomized Set)	SCL001	- Add following information also Medication Category at Study Entry Number of Asthma Exacerbations in the 4 Weeks before Screening, Most Recent Exacerbation: (Treatment, Hospitalization/Emergency Room).	

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.4.4	Reversibility Test (Randomized Set)		The following columns will be presented: - Subject ID - Randomized Treatment - Visit - Assessment Date [Day] - Time of BD Intake - Assessment Time - Assessment Timepoint (Pre-BD, Post-BD) - Parameter (unit) FEV_1 (L) FVC (L) FEV_1 % of predicted (%) Reversibility FEV_1 (mL) Reversibility FEV_1 (%) - Result - Used in Analysis (Y/N)	Footnotes: [1] # COVID-19 diagnosed. [2] * Off-treatment visit.
Listing 16.2.4.5	Training and Diary Dispensation (Randomized Set)	Not available	The following columns will be presented: - Subject ID - Randomized Treatment - Visits (screening and V2) - pMDI inhaler Training? <if no, Specify Reason> - eDiary/Peak Flow Meter Instructions Provided? <if no, Specify Reason>	
Listing 16.2.4.6	Medical and Surgical History (Randomized Set)	MHL001	The following columns will be presented: - Subject ID - Randomized Treatment - System Organ Class - Preferred Term - ID - Start Date - End Date	Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x. [2] Medical/surgical history is defined as conditions in the medical/surgical history and concomitant diseases eCRF form which are not ongoing at Visit 1.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.4.7	Concomitant Diseases (Randomized Set)	MHL002	The following columns will be presented: - Subject ID - Randomized Treatment - System Organ Class - Preferred Term - ID - Start Date - End Date/Ongoing	Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x. [2] Concomitant diseases are defined as conditions in the medical/surgical history and concomitant diseases eCRF form which are ongoing at Visit 1.
Listing 16.2.4.8	Procedures (Randomized Set)	PRL001	- Start and End times to be displayed. - [CAT]: Prior, Concomitant, Post-treatment - Do not display 'Indication' column. - Delete 'Randomized Treatment' and 'Analysis Period'.	Footnotes: [1] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.' [2] Previous procedures: start date < date of first Randomized study medication intake and end date ≤ date of first Randomized study medication intake; [3] Concomitant procedures: date of first Randomized study medication intake ≤ start date < date of last Randomized study medication intake; [4] Post-study procedures: start date ≥ date of last Randomized study medication intake.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.4.9.1	Asthma Medications (Randomized Set)	CML001	- Start and End times to be displayed. - [CAT]: Prior, Concomitant, Post-treatment - Delete 'Analysis Period'.	Footnotes: [1] ATCs and Preferred Name are coded using WHO-DD March 20xx. [2] Previous medication: start date < date of first Randomized study medication intake and stop date ≤ date of first Randomized study medication intake. [3] Concomitant medication: date of first Randomized study medication intake ≤ start date < date of last Randomized study medication intake [4] Post-study medication: start date ≥ date of last Randomized study medication intake. [5] [CAT]: C = Concomitant; P = Previous; PT = Post-treatment.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.4.9.2	Non-Asthma Medications (Randomized Set)	CML001	- Start and End times to be displayed. - [CAT]: Prior, Concomitant, Post-treatment - Delete 'Analysis Period'.	Footnotes: [1] ATCs and Preferred Name are coded using WHO-DD March 20xx. [2] Previous medication: start date < date of first Randomized study medication intake and stop date ≤ date of first Randomized study medication intake. [3] Concomitant medication: date of first Randomized study medication intake ≤ start date < date of last Randomized study medication intake [4] Post-study medication: start date ≥ date of last Randomized study medication intake. [5] [CAT]: C = Concomitant; P = Previous; PT = Post-treatment.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.5.1	Run-in Medication Administration during Run-in Period and Compliance (Randomized Set)	Not available	Variables to be listed: - Subject ID - Randomized Treatment - Date V1 - Date of start of randomized period - Extent of exposure (Days) - Number of scheduled doses - Date of first Run-in study medication intake - Date of last Run-in study medication intake - Number of administered doses - Compliance (%) - Compliance categorical (%)	
Listing 16.2.5.2	Study Drug Administration at Clinic (Randomized Set)	Not available	Variables to be listed: - Subject ID - Randomized Treatment - Actual Treatment - Visit - Study Drug dispensed *(yes/no/specifications)* - Date/Time of Administration [Day] - Number of Inhalations	
Listing 16.2.5.3	Randomized Study Medication Extent of Exposure and Compliance (Randomized Set)	Not available	The following columns will be presented: - Subject ID - Randomized Treatment - Actual Treatment - Period - Date of First Study Drug Intake - Date of Last Study Drug Intake - Extent of Exposure (days) - Number of Scheduled Doses - Number of Administered Doses - Compliance (%) - Compliance categorical (%)	Footnotes: [1] Extent of exposure during entire treatment period (days) = Date of last randomized study medication intake – date of first randomized study medication intake + 1. [2] Compliance = (Total number of administered doses / total number of scheduled doses)*100.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.5.4	Wash-out Prior to Visits (Randomized Set)	Not available	The following columns will be presented: - Subject ID - Randomized Treatment - Prior to Visit V1-V5 and/or ETD - Type of Visit- Wash-out Respected? (Yes/No)	Footnotes: [1] * Off-treatment visit. [2] ° Remote visit. [3] ETD = Early Treatment Discontinuation

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.6.1.1	Spirometry Results at Clinic Visits (Randomized Set)	Not available	Variables to be listed: - Subject ID - Randomized Treatment - Parameter (Unit) - Visit (2,3,4,5) - Timepoint - Assessment Date/Time [Day] - Result - Used in Analysis Parameters are: - FEV_1 (L) - FEV_1 % of predicted (%) - LLN of FEV_1 (L) - FVC (L) - FVC % of predicted (%) - LLN of FVC (L) - FEV_1/FVC (ratio) - FEV_1/FVC % of predicted (%) - FEF 25-75% (L/s) Timepoints are: - Visit 2: -45 and -15 min pre-dose and 5, 15, 30 min, 1h, 2h, 3h, 6h, 9h, 11.5h and 12h post-dose - Visit 3: pre-dose - Visit 4: pre-dose - Visit 5: -45 and -15 min pre-dose and 5, 15, 30 min, 1h, 2h, 3h, 6h, 9h, 11.5h and 12h post-dose.	Footnotes: [1] * Off-treatment visit [2] ° Remote Visit [3] ^ Reallocated visit

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.6.1.2	Spirometry Derived Variables – Part I (Randomized Set)	Not available	Variables to be listed: - Subject ID - Randomized Treatment - Parameter (Unit) - Visit (2, 3, 4, 5) - Timepoint - Result - Change from baseline Parameters are: - FEV_1 (L) - FVC (L) Timepoints are: - Visit 2: pre-dose, 5, 15, 30 min, 1h, 2h, 3h, 6h, 9h, 11.5h and 12h post-dose - Visit 3: pre-dose - Visit 4: pre-dose - Visit 5: pre-dose, 5, 15, 30 min, 1h, 2h, 3h, 6h, 9h, 11.5h and 12h post-dose.	
Listing 16.2.6.1.3	Spirometry Derived Variables – Part II (Randomized Set)	Not available	Variables to be listed: - Subject ID - Randomized Treatment - Visit - Peak FEV_1 (L) - Peak FEV_1 (L) Change from Baseline - FEV_1 $AUC_{0\text{-}12h}$ (L) - FEV_1 $AUC_{0\text{-}12h}$ (L) Change from Baseline - Trough FEV_1 (L) - Trough FEV_1 (L) Change from Baseline - Pre-dose FEV_1 (L) - Pre-dose FEV_1 (L) Change from Baseline Visits are: - Baseline, Visit 2, Visit 3, Visit 4, Visit 5	

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.6.1.4	Spirometry Derived Variables – Part III (Randomized Set)	Not available	Variables to be listed: - Subject ID - Randomized Treatment - Visit - Pre-dose FEV_1 responder (yes/no) - Change from Baseline in Pre-dose FEV_1 (L) - Trough FEV_1 responder (yes/no) - Change from Baseline in Trough FEV_1 (L) Visits are: - Visit 2, Visit 3, Visit 4, Visit 5	
Listing 16.2.6.2	Compliance to the e-Diary (Randomized Set)	Not available	The following columns will be presented: - Subject ID - Randomized Treatment - Period (Run-in /Treatment) - Intervisit period - Number of Valid Session - Number of sessions in period - Compliance (%) - Compliance categorical (%)	

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.6.3.1	Asthma Exacerbations – Part 1 (Randomized Set)	Not available	The following columns will be presented: - Subject ID - Randomized Treatment - Start Date [Day]/End Date [Day] *(add * flag if off-treatment Asthma exacerbation)* - Asthma Exacerbation No. - Severity *(Moderate or Severe)* - How Was the Exacerbation Detected? *(add the Specification if Other)* - Treatment *(list all the treatments taken)* - Duration of Treatment with Systemic Corticosteroids (days) [2] *(display as xx; if no value at all leave blank but otherwise display '-' when no duration)* - Hospitalized/Emergency Room? *(display as xx/xx)* - Date/Time of Admission/Date/Time of Discharge - Duration of Hospitalization (days)	Footnotes: [1] * Off-treatment Asthma exacerbation. [2] Duration corresponds to the duration of all treatments with systemic corticosteroids for the exacerbation

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.6.3.2	Asthma Exacerbations – Part 2 (Randomized Set)	-	The following columns will be presented: - Subject ID - Randomized Treatment - Start Date [Day] *(add * flag if off-treatment exacerbation)* - End Date [Day] - Asthma Exacerbation No. - Medical Procedures Performed *(list all procedures (ticked) performed and the results in brackets)* - Exacerbation Etiology *(if extrapulmonary comorbidities or Other add the Details and/or Specifications in brackets)*	Footnotes: [1] * Off-treatment Asthma exacerbation.
Listing 16.2.6.3.4	Asthma Exacerbations – AE Assessment (Randomized Set)	Not available	The following columns will be presented: - Subject ID - Randomized Treatment - Start Date [Day] *(add * flag if off-treatment Asthma exacerbation)* - End Date [Day] - Asthma Exacerbation No. - SAE? - Related to Study Drug - Outcome - AE Intensity - Action Taken with Study Drug	Footnotes: [1] # COVID-19 diagnosed. [2] § Vaccinated against COVID-19. [3] * Off-treatment period.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.6.4	Electronic Peak Flow Meter: PEF Derived Data (Randomized Set)	Not available	Variables to be listed: - Subject ID - Randomized Treatment - Period (i.e., Baseline, V3-V4 etc., entire treatment period) - Average pre-dose morning PEF: Value and Change From - Baseline - Average pre-dose evening PEF: Value and Change From Baseline,	Footnotes: [1] Data are sorted by subject no., period. [2] In the "period" column, re-allocated visits are considered for the inter-Visit period.
Listing 16.2.6.5	E-Diary: Rescue Medication Derived Data (Randomized Set)	-	Variables to be: - Subject ID - Randomized Treatment - Period (i.e., Baseline, V3-V4 etc., entire treatment period) - Average Use Of Rescue Medication (Number Of Puffs/Days): Actual Value and Change From Baseline, - Percentage of Rescue Use-Free Days: Actuals Value and Change From Baseline.	Footnotes: [1] Data are sorted by subject no., period [2] In the "period" column, re-allocated visits are considered for the inter-visit period

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.6.6	E-Diary: Asthma Symptom Scores Derived Data (Randomized Set)	-	Variables to be listed: - Subject ID - Randomized Treatment - Period (i.e., Baseline, V2-V3, V3-V4 etc., entire treatment period) - Morning (Day-Time) Asthma Symptoms Score: Actual Value (Average) and Change From Baseline - Evening (Night-Time) Asthma Symptoms Score: Actual Value (Average) and Change From Baseline - Percentage of Asthma Free-Days Symptoms: Actual Value (Average) and Change From Baseline	Footnotes: [1] Data are sorted by subject no., period [2] In the "period" column, re-allocated visits are considered for the inter-visit period
Listing 16.2.6.7	ACQ-5/7 Questionnaires (Randomized Set)	Not available	Variables to be listed: - Subject ID - Randomized Treatment - Visits (included Unscheduled) - Date of Visit - Item 1 to 7 Score - ACQ-5 Score: Actuals Value, Change from Baseline and Response - ACQ-7 Score: Actuals Value and Change from Baseline and Response	Footnote: [1] Used in the analysis
Listing 16.2.7.1	Pre-Treatment Adverse Events (Enrolled Set)	AEL001	- Remove pattern	Footnote: [1] An AE is classified as pre-treatment AE if it starts after the informed consent signature and before the first randomized study medication intake.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.7.2	Treatment Emergent Adverse Events (Randomized Set)	AEL002	- Remove pattern	Footnotes: [1] # COVID-19 diagnosed. [2] § Vaccinated against COVID-19. [3] * Off-treatment period. [4] D1 = is the Study Day at Onset Date calculated with reference to the date of first randomized treatment administration [5] D2 = is the Study Day at End Date calculated with reference to the date of first randomized treatment administration [6] System Organ Class and Preferred Term are coded using MedDRA Version xx.x.'. [7] An AE is classified as TEAE if it starts on or after the first Randomized study medication intake up to 1 week after the date of last randomized study medication intake (date of first randomized study medication intake ≤ AE onset date ≤ date of [last randomized study medication intake + 7 Days]).
Listing 16.2.7.3	Serious Treatment Emergent Adverse Events (Randomized Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2
Listing 16.2.7.4	Non-Serious Treatment Emergent Adverse Events (Randomized Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.7.5	Treatment Emergent Adverse Drug Reactions (Randomized Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2. Footnote: [1] # COVID-19 diagnosed. [2] § Vaccinated against COVID-19. [3] An ADR is an AE judged as having a reasonable possibility of relatedness to the study medication.
Listing 16.2.7.6	Serious Treatment Emergent Adverse Drug Reactions (Randomized Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2. Footnote: [4] An ADR is an AE judged as having a reasonable possibility of relatedness to the study medication.
Listing 16.2.7.7	Severe Treatment Emergent Adverse Events (Randomized Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2
Listing 16.2.7.8	Treatment Emergent Adverse Events Leading to Study Drug Discontinuation (Randomized Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2
Listing 16.2.7.9	Treatment Emergent Adverse Events Leading to Death (Randomized Set)	AEL002	Same as Listing 16.2.7.2	Same as Listing 16.2.7.2
Listing 16.2.7.10	Class-Related Treatment Emergent Adverse Events (Randomized Set)	AEL002	Same as Listing 16.2.7.2 - Replace column “System Organ Class / Preferred Term / Reported Term” with “Medical Concept 1 / Medical Concept 2 / Reported Term”.	Same as Listing 16.2.7.2
Listing 16.2.7.11	Post Study Adverse Events (Randomized Set)	AEL001	Same as Listing 16.2.7.1	Same as Listing 16.2.7.1. Footnote: [1] An AE is classified as a post-study AE if it starts 1 week later than the last Randomized study medication intake (AE onset date > date of [last randomized study medication intake + 7 Days]).

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.8.1	Vital Signs (Randomized Set)	VSL002	- Present systolic and diastolic BP, pulse rate and weight. - Remove 'Analysis Period', 'Study Day in Period', 'Change from Pre-dose' and present 'Randomized Treatment' in place of 'Actual Treatment'. - Change 'Analysis Timepoint' to 'Visit' - Add the column 'Re-allocated Visit' after the 'Visit' column *(display ^ after the visit name if visit is re-allocated in 'Visit' column)*. - Add the column 'Assessment Timepoint' after 'Assessment date/time (Study Day)' to display pre/post dose timepoints. - In the header, update the footnote number as per 'Footnotes' list.	Footnotes: [1] # COVID-19 diagnosed. [2] ^ Re-allocated data. [3] Baseline=Y flags baseline value. [4] USE=Y: included in the analysis.
Listing 16.2.9.1	ECG (Randomized Set)	EGL002	- Present HR, QTcF, PR, QRS, investigator interpretation and central reading interpretation. - Remove 'Analysis Period', 'Study Day in Period', and present 'Randomized Treatment' in place of 'Actual Treatment'. - Change 'Analysis Timepoint' to 'Visit' - Add the column 'Re-allocated Visit' after the 'Visit' column *(display ^ after the visit name if visit is re-allocated in 'Visit' column)*. - Add the column 'Assessment Timepoint' before 'Assessment date/time (Study Day)' to display pre/post dose timepoints. - In the header, update the footnote number as per 'Footnotes' list.	Footnotes: [1] # COVID-19 diagnosed. [2] ^ Re-allocated data. [3] Baseline = Y flags baseline value. [4] USE=Y: included in the analysis [5] ETD = Early Treatment Discontinuation [6] CS = Clinically Significant; NCS = Non Clinically Significant

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.9.2	ECG Abnormalities (Randomized Set)	EGL002	- Display only subjects with ECG abnormalities. -Remove "Study Day in Period". - Remove 'Analysis Period' column and present 'Randomized Treatment' in place of 'Actual Treatment'. - Update 'Analysis Timepoint' column to be 'Visit'. - Add the column 'Re-allocated Visit' after the 'Visit' column *(display ^ after the visit name if visit is re-allocated in 'Visit' column)*. - Add the column 'Assessment Timepoint' after 'Assessment date/time (Study Day)' to display pre/post dose timepoints. - In the header, update the footnote number as per 'Footnotes' list. - Last three columns are: "Result" (with possible flags [A1] or [A2] or [A3]) "Change from baseline" (with possible flags [H1] or [H2]) "Change from pre-dose" (with possible flags [H1] or [H2])	Footnotes: [1] # COVID-19 diagnosed. [2] ^ Re-allocated data. [3] Baseline = Y flags baseline value. [4] USE=Y: included in the analysis [5] ETD = Early Treatment Discontinuation [A1] For Male, Absolute QTcF >450 ms. [A2] Absolute QTcF >480 ms for male or Absolute QTcF >470 ms for female. [A3] Absolute QTcF >500 ms. [H1] Substantial increase in QTcF from baseline/pre-dose of >30 ms [H2] Substantial increase in QTcF from baseline/pre-dose >60 ms.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.9.3	ECG Interpretation and Findings (Randomized Set)	EGL002	- Display only subjects with ECG abnormalities. -Remove "Study Day in Period". - Include as test the ECG interpretation (ECG investigator interpretation and ECG central reading interpretation should be displayed as last parameters at assessment timepoint). - Include as test the ECG findings - Remove 'Analysis Period' column and present 'Randomized Treatment' in place of 'Actual Treatment'. - Update 'Analysis Timepoint' column to be 'Visit'. - Add the column 'Re-allocated Visit' after the 'Visit' column *(display ^ after the visit name if visit is re-allocated in 'Visit' column)*. - Add the column 'Assessment Timepoint' after 'Assessment date/time (Study Day)' to display pre/post dose timepoints. - In the header, update the footnote number as per 'Footnotes' list. Listing will be sorted by Subject ID, Visit, Assessment Date/Time and Test. Report the Test column before the Result column.	Footnotes: [1] # COVID-19 diagnosed. [2] ^ Re-allocated data. [3] Baseline = Y flags baseline value. [4] USE=Y: included in the analysis [5] ETD = Early Treatment Discontinuation [6] CS = Clinically Significant; NCS = Non Clinically Significant
Listing 16.2.10.1	Laboratory Tests: Hematology (Randomized Set)	LBL001	- Remove "Study Day in Period".	Footnotes: [1] Baseline=Y flags baseline value. [2] USE=Y: included in the analysis. [3] H = Abnormally High Value / L = Abnormally Low Value, compared to the Normal Range. [4] CSA = Abnormal, Clinically Significant.

Listing Number	Listing Title	Template Code	Notes	Footnotes
Listing 16.2.10.2	Laboratory Tests: Biochemistry (Randomized Set)	LBL001	- Remove "Study Day in Period".	Footnotes: [1] Baseline=Y flags baseline value. [2] USE=Y: included in the analysis. [3] H = Abnormally High Value / L = Abnormally Low Value, compared to the Normal Range. [4] CSA = Abnormal, Clinically Significant.
Listing 16.2.10.3	Pregnancy Test (Randomized Set)	LBL005	- Remove "Study Day in Period".	
Listing 16.2.11.1	Physical Examination Results (Randomized Set)	PEL001	- Remove "Study Day in Period".	
Listing 16.2.11.2	Oropharyngeal Examination Results (Randomized Set)	PEL001	- Remove "Body System" and "Study Day in Period".	
Listing 16.2.12	Comments	COL001		
Listing 16.2.13	COVID-19 Impact	Not available	Variables to be listed: - Subject ID - Randomized Treatment - AE with COVID-19 Diagnosis - Missing Visits due to COVID-19	
Listing 16.2.14	IC collected	Not available	Variables to be listed: - Subject ID - IC collected (yes/no) - Date of IC collection - Protocol version - IC to secondary data usage (yes/no)	

16.3 Figures

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Listing Number
Figure 14.1.1	Disposition Flow Chart	DSF001		Source: Table 14.1.1.1, Table 14.1.1.2
Figure 14.1.2	Flow Chart of Analysis Sets	DSF003		Source: Table 14.1.1.6
Figure 14.1.3.1	Time To Discontinuation From the Study Treatment (Randomized Set)	Not available	Display Default Kaplan-Meyer Plot: Y axis represent the Probability of Discontinuation, X axis represent the time from baseline to completion/discontinuation with: 0, 4, 8, up to 12 weeks.	Source : Table 14.1.1.4.a
Figure 14.1.3.2	Time To Discontinuation From the Study (Randomized Set)	Not available	Same as Figure 14.1.3.1.	Source : Table 14.1.1.4.b
Figure 14.2.1.1	Adjusted Mean Changes from Baseline (95% CI) FEV_1 $AUC_{0\text{-}12h}$ (L) at Week 0 and Week 12 - Main Estimand (Intention-To-Treat Set)	TPF001	- X-axis represents study planned weeks. - Y-axis represents the adjusted mean change from baseline.	Source : Table 14.2.1.2, Table 14.2.3.1 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).
Figure 14.2.1.2	Forest Plot: Adjusted Mean Differences (95% CI) in Change from Baseline in FEV_1 $AUC_{0\text{-}12h}$ (L) at Week 12 - Main Estimand (Intention-To-Treat Set)	TPF003	- Y-axis represents the pairwise comparisons of treatments. - X-axis represents the adjusted mean difference and the corresponding 95% CI. Display result for ITT set and Subgroups analysis (for all categories of all subgroups) in the same graph. If a subgroup category has < 20 subjects, inferential analysis will not be performed and therefore will not be plotted. A placeholder/label will be shown but with no results.	Source: Table 14.2.1.2, Table 14.2.1.4 to Table 14.2.1.10 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Listing Number
Figure 14.2.1.3	Display of Delta Values from Tipping Point Analysis for Change from Baseline in FEV_1 $AUC_{0\text{-}12h}$ (L) at Week 12 - Main Estimand, Sensitivity Analysis (Intention-To-Treat Set)	Not available	**Page #1 (see SAS code in section 14.8, graphical representation of results #1)** - Title of the plot is "Plot of Statistical Significance" - Display all combinations of delta values by means of dots in a grid. - Y-axis represents the delta value (L) for missing data in CHF 718 arm. - X-axis represents the delta value (L) for missing data in CHF 1535 arm. - Color the points/dots: • In red, those for which the treatment difference is NOT in favor of CHF 1535 arm • In orange, those for which the treatment difference is in favor of CHF 1535 but its p-value ≥ 0.05 • In green, those for which the treatment difference is in favor of CHF 1535 and its p-value < 0.05. - Add legend/label for colors accordingly.	Source: Table 14.2.1.3

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Listing Number
Figure 14.2.1.4	Forest Plot: Adjusted Mean Differences (95% CI) in Change from Baseline in Lung Function Parameters at Week 12 (Intention-To-Treat Set)	TPF003	- Y-axis represents the pairwise comparisons of treatments for the following parameters: • FEV_1 $AUC_{0\text{-}12h}$ (L) normalized by time at Week 12 • Peak FEV_1 (L) within the first 3 hours post-dose at Week 12 • Trough FEV_1 (L)at Week 12 • Pre-dose FEV_1 (L) at Week 12 • Morning PEF (L/min) over 12-week treatment period • Evening PEF (L/min) over 12-week treatment period. - X-axis represents the adjusted mean difference and the corresponding 95% CI.	Source: Table 14.2.1.2, Table 14.2.2.2, Table 14.2.5.2, Table 14.2.6.2 Table 14.2.7.2 and Table 14.2.8.2. Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).
Figure 14.2.2.1	Adjusted Mean Changes from Baseline (95% CI) in peak FEV_1 (L) within the first 3 hours post-dose at Week 0 and Week 12 – Main Estimand (Intention-To-Treat Set)	TPF001	- X-axis represents study planned weeks. - Y-axis represents the adjusted mean change from baseline.	Source : Table 14.2.2.2, Table 14.2.4.1 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Listing Number
Figure 14.2.2.2	Forest Plot: Adjusted Mean Differences (95% CI) in Change from Baseline peak FEV_1 (L) within the first 3 hours post-dose at Week 12 – Main Estimand	TPF003	- Y-axis represents the pairwise comparisons of treatments. - X-axis represents the adjusted mean difference and the corresponding 95% CI. Display result for ITT set and Subgroups analysis (for all categories of all subgroups) in the same graph. If a subgroup category has < 20 subjects, inferential analysis will not be performed and therefore will not be plotted. A placeholder/label will be shown but with no results.	Source: Tables 14.2.2.2, Table 14.2.2.4 to Table 14.2.2.7 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).
Figure 14.2.2.3	Display of Delta Values from Tipping Point Analysis for Change from Baseline in peak FEV_1 (L) within 3 hours post-dose at Week 12 - Main Estimand, Sensitivity Analysis (Intention-To-Treat Set)	Not available	Same as Figure 14.2.1.3	Source: Table 14.2.2.3
Figure 14.2.3	Adjusted Mean Changes from Baseline (95% CI) in trough FEV_1 (L) at Week 0 and Week 12 - Main Estimand (Intention-To-Treat Set)	TPF001	- X-axis represents study planned weeks. - Y-axis represents the adjusted mean change from baseline.	Source : Table 14.2.5.2 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Listing Number
Figure 14.2.4	Adjusted Mean Changes from Baseline (95% CI) in pre-dose morning FEV_1 (L) at Week 4, 8 and 12 - Main Estimand (Intention-To-Treat Set)	TPF001	- X-axis represents study planned weeks. - Y-axis represents the adjusted mean change from baseline.	Source : Table 14.2.6.2 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).
Figure 14.2.5	Adjusted Mean Changes from Baseline (95% CI) in average morning PEF (L/min) over 12-week treatment period (Intention-To-Treat Set)	TPF001	- X-axis represents the following timepoints in order: • [Week 0– Week 4] • [Week 4 – Week 8] • [Week 8 – Week 12] - Y-axis represents the adjusted mean change from baseline.	Source : Table 14.2.7.2 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).
Figure 14.2.6	Adjusted Mean Changes from Baseline (95% CI) in average evening PEF (L/min) over 12-week treatment period (Intention-To-Treat Set)	TPF001	- X-axis represents the following timepoints in order: • [Week 0– Week 4] • [Week 4 – Week 8] • [Week 8 – Week 12] - Y-axis represents the adjusted mean change from baseline.	Source : Table 14.2.8.2 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Listing Number
Figure 14.2.7	Adjusted Odds Ratio (95% CI) for Proportion of pre-dose morning FEV_1 responders at Week 4, 8 and 12 - Main Estimand (Intention-To-Treat Set)	TPF001	- X-axis represents study planned weeks. - Y-axis represents the adjusted odds ratio.	Source : Table 14.2.9.2 Footnotes: [1] Logistic regression model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).
Figure 14.2.8	Adjusted Odds Ratio (95% CI) for Proportion of trough FEV_1 responders at Week 0 and Week 12 - Main Estimand (Intention-To-Treat Set)	TPF001	- X-axis represents study planned weeks. - Y-axis represents the adjusted odds ratio.	Source : Table 14.2.10.2 Footnotes: [1] Logistic regression model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).
Figure 14.2.9	Adjusted Mean Changes from Baseline (95% CI) in ACQ-7 Score at Week 4, 8 and 12 (Intention-To-Treat Set)	TPF001	- X-axis represents study planned weeks. - Y-axis represents the adjusted mean change from baseline.	Source: Table 14.2.11.2 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0, pre-dose) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Listing Number
Figure 14.2.10	Adjusted Mean Changes from Baseline (95% CI) in ACQ-5 Score at Week 4, 8 and 12 (Intention-To-Treat Set)	TPF001	- X-axis represents study planned weeks. - Y-axis represents the adjusted mean change from baseline.	Source: Table 14.2.11.3 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value (i.e., Week 0) as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).
Figure 14.2.11	Adjusted Mean Changes from Baseline (95% CI) in percentage of rescue medication-free days over 12-week treatment period (Intention-To-Treat Set)	TPF001	- X-axis represents the following timepoints in order: • [Week 0– Week 4] • [Week 4 – Week 8] • [Week 8 – Week 12] - Y-axis represents the adjusted mean change from baseline.	Source : Table 14.2.12.2 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).
Figure 14.2.12	Adjusted Mean Changes from Baseline (95% CI) in percentage of asthma symptom-free days over 12-week treatment period (Intention-To-Treat Set)	TPF001	- X-axis represents the following timepoints in order: • [Week 0– Week 4] • [Week 4 – Week 8] • [Week 8 – Week 12] - Y-axis represents the adjusted mean change from baseline.	Source : Table 14.2.13.2 Footnotes: [1] ANCOVA model includes treatment, region, and prior asthma therapy as fixed effects, and baseline value as covariate. [2] Missing data are imputed using available off-treatment data (or a CR imputation).

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Listing Number
Figure 14.3.1	Forest plot: General TEAEs (Safety Set)	Not available	The figure will consist of two panels: Left panel will display a dot plot: - Y axis presents each type of TEAE by treatment and event occurred in at least 5 subjects: TEAE, SAE, ADR, SADR, severe AE, AE leading to discontinuation, AEs leading to death. - X axis represents the proportion of each type of Class-Related TEAE Right panel will display a forest plot: - Y axis presents each type of TEAE by treatment and event occurred in at least 5 subjects: TEAE, SAE, ADR, SADR, severe AE, AE leading to discontinuation, AEs leading to death. - X axis represents the Risk Difference (95% CI) of each type of Class-Related TEAE Analysis to be made only if only the event occurred in at least 5 subjects.	Source: Table 14.3.2.10 Footnote: [1] The comparative analysis (i.e., estimation of risk difference and its 95% CI) will not be carried out if the total number of subjects with the event in the overall Safety Set is < 5.

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Listing Number
Figure 14.3.2	Forest plot: TEAEs by SOC (Safety Set)	Not available	The figure will consist of two panels: Left panel will display a dot plot: - Y axis presents each TEAE by treatment and by SOC and event occurred in at least 5 subjects. - X axis represents the proportion of each type of Class-Related TEAE Right panel will display a forest plot: - Y axis presents each TEAE by treatment and by SOC and event occurred in at least 5 subjects. - X axis represents the Risk Difference (95% CI) of each type of Class-Related TEAE Analysis to be made only if only the event occurred in at least 5 subjects.	Source: Table 14.3.2.11 Footnote: [1] The comparative analysis (i.e., estimation of risk difference and its 95% CI) will not be carried out if the total number of subjects with the event in the overall Safety Set is < 5.
Figure 14.3.3	Forest plot: TEAEs by PT (Safety Set)	Not available	The figure will consist of two panels: Left panel will display a dot plot: - Y axis presents each TEAE by treatment and by PT and event occurred in at least 5 subjects. - X axis represents the proportion of each type of Class-Related TEAE Right panel will display a forest plot: - Y axis presents each TEAE by treatment and by PT and event occurred in at least 5 subjects. - X axis represents the Risk Difference (95% CI) of each type of Class-Related TEAE Analysis to be made only if only the event occurred in at least 5 subjects.	Source: Table 14.3.2.11 Footnote: [1] The comparative analysis (i.e., estimation of risk difference and its 95% CI) will not be carried out if the total number of subjects with the event in the overall Safety Set is < 5.

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Listing Number
Figure 14.3.4	Forest plot: General Class-related TEAEs (Safety Set)	Not available	The figure will consist of two panels: Left panel will display a dot plot: - Y axis presents each type of Class-Related TEAE by treatment and event occurred in at least 5 subjects: TEAE, SAE, ADR, SADR, severe AE, AE leading to discontinuation, AEs leading to death. - X axis represents the proportion of each type of Class-Related TEAE Right panel will display a forest plot: - Y axis presents each type of Class-Related TEAE by treatment and event occurred in at least 5 subjects: TEAE, SAE, ADR, SADR, severe AE, AE leading to discontinuation, AEs leading to death. - X axis represents the Risk Difference (95% CI) of each type of Class-Related TEAE Analysis to be made only if only the event occurred in at least 5 subjects.	Source: Table 14.3.2.21 Footnote: [1] The comparative analysis (i.e., estimation of risk difference and its 95% CI) will not be carried out if the total number of subjects with the event in the overall Safety Set is < 5.

Figure Number	Figure Title	Template Code	Notes	Footnotes/Source Listing Number
Figure 14.3.5	Forest plot: Class-Related TEAEs by Medical Concept 1 (Safety Set)	Not available	The figure will consist of two panels: Left panel will display a dot plot: - Y axis presents each Class-Related TEAE by treatment and by Medical Concept 1 and event occurred in at least 5 subjects. - X axis represents the proportion of each type of Class-Related TEAE Right panel will display a forest plot: - Y axis presents each Class-Related TEAE by treatment and by Medical Concept 1 and event occurred in at least 5 subjects. - X axis represents the Risk Difference (95% CI) of each type of Class-Related TEAE Analysis to be made only if only the event occurred in at least 5 subjects.	Source: Table 14.3.2.22 Footnote: [1] The comparative analysis (i.e., estimation of risk difference and its 95% CI) will not be carried out if the total number of subjects with the event in the overall Safety Set is < 5.
Figure 14.3.6	Forest plot: Class-Related TEAEs by Medical Concept 2 (Safety Set)	Not available	The figure will consist of two panels: Left panel will display a dot plot: - Y axis presents each Class-Related TEAE by treatment and by Medical Concept 2 and event occurred in at least 5 subjects. - X axis represents the proportion of each type of Class-Related TEAE Right panel will display a forest plot: - Y axis presents each Class-Related TEAE by treatment and by Medical Concept 2 and event occurred in at least 5 subjects. - X axis represents the Risk Difference (95% CI) of each type of Class-Related TEAE Analysis to be made only if only the event occurred in at least 5 subjects.	Source: Table 14.3.2.22 Footnote: [1] The comparative analysis (i.e., estimation of risk difference and its 95% CI) will not be carried out if the total number of subjects with the event in the overall Safety Set is < 5.

APPENDIX I

US Geography Division

Since 1950, the United States Census Bureau defines four statistical regions, with nine divisions:

- Region 1: **Northeast**
  - Division 1: New England (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont)
  - Division 2: Mid-Atlantic (New Jersey, New York, and Pennsylvania)
- Region 2: **Midwest**
  - Division 3: East North Central (Illinois, Indiana, Michigan, Ohio, and Wisconsin)
  - Division 4: West North Central (Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota)
- Region 3: **South**
  - Division 5: South Atlantic (Delaware; Florida; Georgia; Maryland; North Carolina; South Carolina; Virginia; Washington, D.C. and West Virginia)
  - Division 6: East South Central (Alabama, Kentucky, Mississippi, and Tennessee)
  - Division 7: West South Central (Arkansas, Louisiana, Oklahoma, and Texas)
- Region 4: **West**
  - Division 8: Mountain (Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, and Wyoming)
  - Division 9: Pacific (Alaska, California, Hawaii, Oregon, and Washington)

Puerto Rico and other US territories are not part of any census region or census division.

Source: *United States Census Bureau, Geography Division. "Census Regions and Divisions of the United States"* [14]